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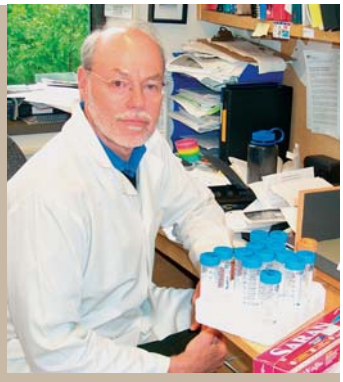
Phillip Sharp discusses RNAi, Nobel Prizes and entrepreneurial science

Interviewed by Christopher Watson



Phillip A. Sharp
Institute Professor, Center for Cancer Research, MIT

Phillip A. Sharp is currently Institute Professor and member of the Center for Cancer Research at the Massachusetts Institute of Technology (MIT). His landmark achievement was the discovery of RNA splicing in 1977. This work provided one of the first indications of the startling phenomenon of 'discontinuous genes' in mammalian cells and won him the 1993 Nobel Prize in Physiology or Medicine. Dr. Sharp has authored over 300 scientific papers and serves on many scientific advisory boards and committees, including the National Cancer Institute's Advisory Board, which he chaired for two years (2000–2002), the Sloan Foundation Board of Trustees (1995–2004), and the Ludwig Institute for Cancer Research. His work has been honored with numerous awards including the Gairdner Foundation International Award, General Motors Research Foundation Alfred P. Sloan, Jr. Prize for Cancer Research, Louisa Gross Horwitz Prize and Albert Lasker Basic Medical Research Award. He is an elected member of the National Academy of Sciences, the Institute of Medicine and the American Academy of Arts and Sciences. Dr. Sharp earned a B.A. degree from Union College, KY, and a PhD in chemistry from the University of Illinois. He co-founded Biogen, Inc. (now Biogen Idec) in 1978 and Alnylam Pharmaceuticals in 2002. Dr. Sharp spent most of his scientific career at MIT where he also assumed administrative roles, as Director of the Center for Cancer Research, Head of the Department of Biology and, until recently, Founding Director of the McGovern Institute.

What made you pursue a career in science?
As a young person I was fascinated about learning, about science and scientific advances. It was a field that satisfied me because it provided a format and a framework to obtain answers that I could understand and investigate by experimentation.

You started your career by studying chemistry and mathematics. Is there another career path you might have chosen had you not discovered the attractions of molecular biology?
I enjoyed chemistry and mathematics but as I learned about the status of knowledge in molecular biology I became fascinated with it. If I had pursued another career path it probably would have been in chemistry, probably in the academic arena, but I am glad I didn't do that! The questions in molecular biology are profound and a very interesting aspect of this research was its contribution to our understanding of the human condition. I entered the field of molecular biology just at the stage where it could begin to look at the genetic, cell biological and molecular aspects of the human organism – learning about humanity and human existence by understanding the biological basis of it. I still think that this is one of the most fascinating aspects of biological science, particularly neuroscience, where we are beginning to understand the most human aspect of life science – how our brain works.

You did postdoctoral research at Cold Spring Harbour (CSH) under the mentorship of James Watson. What are your memories of that time in the early 1970s?
Jim launched the CSH effort around the study of the role of viruses in causing cancer. He had hired a group of exciting young investigators at CSH, Joe Sambrook being the one I collaborated most closely with. Jim clearly set the style for the lab that 'today is better than tomorrow' if you are going to do something, and also emphasized the importance of trying to do something significant. He always projected the people in the lab as being among the best in the field, which gave you a confidence when approaching particular

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research areas and interacting with other scientists. It was a very exciting time because so little was known.

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You have co-founded two leading biotech companies. What factors drove you to start a company?

When founding Biogen with my colleagues, it was a time when there was a lot of technology in the academic world, such as recombinant DNA, and an appreciation of the practical consequences of these, but the technology was not translated to the private sector where it could be nurtured, focused and brought to fruition. We anticipated that there would be a whole industry established by this technology. Participating in this translation was a rare opportunity, and it was a lot of fun. I got to know business people, business structures and motivations, as well as other aspects of society that I would not have seen otherwise. In addition, I was able to work with a group of young, talented people, and help them apply their knowledge to improving other people's lives. Biogen was successful with a number of products, including Hepatitis B vaccine and α and β-interferon. Therefore, I've probably touched more people's lives directly through my involvement as an entrepreneur in Biogen than I have with my science and this has been very gratifying. It is a similar situation with Alnylam. There was a new scientific discovery (RNAi) that large companies didn't understand and a number of exciting young colleagues to work with who had the interest and commitment to undertake a really focused effort to develop this technology as a therapeutic. We realised that RNAi is a technology that, if it works, will impact on a vast number of human diseases. I felt starting Alnylam would be fun and important.

Biogen and Alnylam were founded in very different eras – Biogen in the late 70s when it was very much a pioneering company and Alnylam more recently when the industry was more mature. What were the major differences you experienced when establishing these companies?

With Biogen in the late 1970s a whole industry had to be created and the whole concept and financial structure of biotech was not clear. Now, 25 years later, we have people who grew up with biotech, who know about the financing, the translational aspects, the relationships with large pharmaceutical companies and so on. It is therefore easier to find people who can work in such an organisation. When founding Biogen, we did not hire a single person who had experience in pharmaceutical translation, except at the CEO level. In Alnylam's case, we did not hire a single person without that experience. Back in the Biogen days you had to tell people that they were part of a private company, tell them what that meant, and explain what stock options are and so on. Those challenges are no longer there. However, it is still a challenge to take a new technology and make it successful.

The biotech sector is seen by many as the most innovative and productive segment of the industry. What value do you think the sector has added to the pharmaceutical industry over the last 20 years or so?

It has contributed $59 billion dollars worth of protein products! It has been an incredibly innovative sector. Let's look at some of the successes. High quality human insulin has been produced, which has benefited an enormous number of lives, human growth hormone, interferons, which have been a godsend to people who have reoccurring Hepatitis C and B infections. We have Hepatitis B vaccine and erythropoietin, which have really changed lives. With a number of products based on monoclonal antibodies, we are close to being able to control many autoimmune diseases. Inroads have been made into cancer. There is clearly more to do here but the community has now accepted that the new pharmaceuticals in cancer are going to target specific genes, have less side-effects, greater efficacy and will be more specific to a type of cancer. The biotech sector has had a huge impact on people's lives and will continue to do so for decades to come.

Smaller companies are often said to have significant advantages over their larger more established brethren (e.g. more agile and efficient). As you have seen Biogen become more successful and increase in size have you seen it become encumbered by the same difficulties that affect larger, older pharmaceutical companies?

Biogen is still a relatively small company, it's nothing like a Merck or a Pfizer where you have 50 000 or 100 000 employees scattered around the world but clearly there is a lot more bureaucracy when you are running a company that has 4–5000 people compared with running a company that has 50 people. Being able to manage and motivate people and make quick decisions is much more difficult as a company grows. Keeping the objectives of the company in terms of its culture and standards of excellence are real management challenges. When you have 50 people it's a big advantage bringing everybody into one room and communicating with them and this is one reason that small companies can be much more innovative in terms of the science. Making decisions on a fairly short timescale and having a lot of people input creatively and decide on a focus before making a decision gives a small company an advantage.

'With Biogen in the late 1970s a whole industry had to be created'

If there is a single piece of advice you would give to entrepreneurial scientists looking to start up a company what would it be?

I think it would be two things. One is that the business side is at least as important as the science. If you don't have really good business input you can't be successful. The second thing I would say is that you have to look at the science and be sure that it is really new and that, if successful, the approach will create value in the context of translation. You have to be very critical about what you are willing to spend your time on to make that translation work. In both the cases I have been involved with, it was a totally new technology and larger established companies were not involved in the technology so we were at least on a level playing field, i.e. had as great a probability of success as anybody else.

There have been few technologies that have fired the enthusiasm of scientific community and pharmaceutical companies as much as

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RNAi has. When do you envisage therapeutics made from this approach surfacing?

The term RNAi was first coined in 1998 and the first companies were established in about 2002. I would hope that by 2007, maybe 2009, that we will start to see products. That is a very fast track! I think the technology is really exciting. You have to critically assess the published research but there has been some good news. I think the work on systemic administration that Alnylam has just published is a very nice piece of work, suggesting that the delivery problem is surmountable by chemistry and ingenuity [1]. There is also some other really interesting work so I think we are beginning to see signs of this technology advancing. I can't say that it is certain that this approach will be successful but I'm hopeful.

'People in the physical and chemical sciences frequently don't appreciate the incompleteness of our understanding of human cell biology.'

The recent paper by researchers at Alnylam demonstrating that intravenous injection of a chemically modified siRNA could silence an endogenous gene encoding apolipoprotein B (apoB) in mice represents a breakthrough in solving some of the issues associated with stability and delivery of RNAi to tissues. What do you think the impact of this research will be to the RNAi field?

I believe it will have significant implications. They saw activity in the liver by every definition – they saw the drug there, there was silencing of apoB messenger RNA, decreased plasma levels of apoB protein and reduced total cholesterol – it's an incredible piece of science. It involved systemic delivery under conditions that would be consistent with treatment in humans but it did involve very high doses so that is going to have to be addressed. It was also an acute treatment so there are questions about how long you can treat and so on. So, it is a very important statement but certainly not a statement that says this is definitely how the approach is going to work. When we started this effort we did not know how delivery might be approached and I think this indicates an important way of thinking about these problems. Delivery to other tissues, stability and efficacy are all issues we will have to work through. At the end of the day we will not know if the approach will work until we go into the human disease setting and see if there is an effect on the disease.

What is your opinion of the RNAi patent landscape? There have been some lawsuits and challenges in the last year or so concerning who owns key aspects of RNAi technology. How will this affect the field, particularly with regard to getting RNAi therapeutics to the bedside?

Some patents are currently being considered by various patent agencies. Most of these haven't been issued as of yet and we will only obtain a clear picture once this happens. This said, I think Alnylam has a very strong patent position, involving the earliest developments in RNAi, to the point of cross-licensing with ISIS Pharmaceuticals and having access to all of their chemistry, which is a patent estate that is just breathtaking! I expect that intellectual property is going to be important, as it is in any pharmaceutical field, and hopefully we will avoid dissipating ourselves in litigation and find ways to discipline the market and allow the development of new pharmaceuticals in this space.

You are renowned for your work on RNA splicing. There is an increasing awareness of the role of splicing in human pathologies. What do you think are the prospects for molecular therapies that target alternative splicing?

With the availability of genomic data more is being learned about the role of alternative splicing in the activities of different genes. The most recent work indicates that maybe 10% of genes are alternatively spliced in an evolutionarily conserved manner, meaning that the same exon is being alternatively spliced in mouse, humans and even in other organisms. I think that this evolutionarily conserved subset of alternative splicing is very strong evidence that this process plays a deep and important role in the organism. So we are now beginning to appreciate the differing importance of various alternative splicing reactions in human physiology. It is somewhat surprising that we do not have a better understanding of the nature of the gene products involved in controlling alternative splicing but this is starting to emerge. This may offer therapeutic approaches through modulating alternative splicing; we believe that these processes are highly dependent on protein modifications involving kinases and phosphatases. It seems possible that small molecule inhibitors might be able to modulate alternative splicing and impact on disease. However, these processes have not yet been well enough defined at the molecular level to allow significant effort in this area.

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The core drug discovery technologies and processes (i.e. microarrays) tend, on the whole, to ignore alternative splicing. What are the consequences of overlooking these variants to future drug discovery efforts?

Like many things in biology, we tend to de-emphasise things we don't know much about. In biology we emphasize our knowledge of specifics and then meld these together into a conceptual framework and don't discuss the lack of knowledge in certain areas. People in the physical and chemical sciences frequently don't appreciate the incompleteness of our understanding of human cell biology. Alternative splicing is part of that large body of knowledge that we only now are developing some of the tools to understand. There is no better illustration of the lack in depth of knowledge in some areas of cell biology than the fact that RNAi was not discovered until 1998! It is clear now that there are a minimum of 250 microRNA genes in our genome and they are involved in important things such as control of development, they are likely to be involved in celltype specific activities in the liver, brain and muscle – it's remarkable how ubiquitous they are and yet we didn't even know they existed until 2001! There are just great voids of knowledge. It's the same with alternative splicing – we don't focus on it because we don't know how to control it and when drugs

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work on a target that is alternatively spliced it's an added complication.

Your work, along with that of Richard Roberts, in this area led to you being awarded the Nobel Prize. To the majority of scientists such recognition would represent a career zenith. Is there a problem with career motivation after receiving such an accolade?

Clearly there are many ways to motivate oneself and I've always sought to have as interesting life as I could find. I was not motivated by the thought of winning specific prizes but I have been very generously rewarded in terms of accolades. The Nobel Prize is a wonderful experience and an incredible honor, and there was a point when I said 'I have done great science, it has been acknowledged, it has had a big impact, can that ever be duplicated?' The answer is probably no. So what happens then? Many people spend their time providing leadership so that another generation of scientists can make contributions and I've done that by being Head of the Department of Biology and founding director of the McGovern Institute at MIT. In addition, I wanted to try to continue to do active research because it's something I find very enjoyable. It's a way of contributing and interacting with people around the world. You do step back and think about what your career motivations are. People take different tracks but that is the path I have taken.

How do you see basic academic research contributing to the development of therapeutics in the future, particularly in light of FDA and NIH translational research initiatives?

It has historically been the case, and is increasingly the case now, that the NIH and Federal agencies have provided the support for much of the discovery research in the pharmaceutical space. With the investment the country has made and the intent of that investment in benefiting the quality of life of the citizens of this country, translation of scientific knowledge into therapeutics is something that needs to be as efficient as possible. I believe that what we are seeing in terms of translational emphasis is part of trying to gain the benefit of that large investment. I am of the opinion that it is almost impossible for a Federal agency to develop a drug. It requires an incredible amount of focus, even to be as inefficient as the private sector is now. An enormous amount of dollars is invested per drug created by the pharmaceutical world. Much of this is due to the cost of clinical trials and failure at the clinical trial level. We have just seen really sophisticated companies developing sophisticated drugs such as Vioxx that enter the market and still run into problems with side-effects. Therefore, this is a complicated business and I don't think that you can take Federal-type resources that are typically diffuse and need to be dealt with in terms of accountability and peer-review, and make drugs. I think that translation by Federal agencies is preparing the transfer of drug development to private organisations.

Who has been your greatest inspiration?

I have been inspired by a host of people, wonderful teachers in high school, Victor Bloomfield my graduate mentor, Norman Davidson who was a special mentor during my postdoctoral period at CalTech, Jim Watson and Joe Sambrook during my time at CSH. At MIT I have benefited enormously from a number of colleagues, particularly David Baltimore, who has been a great friend, collaborator, and inspiration. In the private sector I have had interactions with many highly talented people. Jim Vincent had a tremendous impact on my life during the development of Biogen, as did Wally Gilbert, Charles Weissmann and Kenneth Murray. They were all inspirations as scientific colleagues and peers so I've had a wonderful series of interactions and support from colleagues.

References

1 Soutschek, J. *et al.* (2004) Therapeutic silencing of an endogenous gene by systematic administration of modified siRNAs. *Nature* 432, 173–178

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