Stuart Schreiber: biology from a chemist's perspective

Interview by Joanna Owens

Stuart L. Schreiber, Morris Loeb Professor, Howard Hughes Medical Institute Investigator, and Chair of the Department of Chemistry and Chemical Biology at Harvard University

Stuart L. Schreiber is Morris Loeb Professor and Chair of the Department of Chemistry and Chemical Biology at Harvard University, and an Investigator at the Howard Hughes Medical Institute. He founded Harvard's ICCB and directs the NIH-funded Initiative for Chemical Genetics (ICG). He is also a faculty member of the Broad Institute, a joint initiative by Harvard University and MIT that is 'dedicated to leveraging different disciplines to create a new toolkit for genomic medicine'.

Following doctoral studies at Harvard University in the laboratory of R. B. Woodward and Y. Kishi, he joined the faculty at Yale University in 1981, where he was promoted to Full Professor in 1986. In 1988, he returned to Harvard, where, in addition to his main roles described above, he is an affiliate of both the Harvard Department of Molecular and Cellular Biology and Harvard Medical School Department of Cell Biology. He is also a member of the Graduate Programs in Biophysics at Harvard University and in Immunology at the Harvard Medical School.

In keeping with his multiple roles at Harvard, Schreiber is renowned for taking an integrative and systematic approach to exploring biology. His pioneering work in the field of chemical biology has resulted in the characterisation of many cellular pathways, including (in collaboration with researchers at Stanford University) the identification of the calcium–calcineurin–NFAT signalling pathway [1]. His lab has developed several methodologies including diversity-oriented synthesis (DOS) [2,3] and in 2003 launched the Chembank public database (http://chembank.med.harvard.edu), a suite of informatic tools and databases to promote the use of chemical genetics.

Schreiber has received many awards and honours including the Tetrahedron Prize for Creativity in Organic Chemistry (1997) and most recently the Society for Biomolecular Screening Achievement Award (2004). He has founded several successful biotechnology firms, including Vertex Pharmaceuticals in 1989, ARIAD Pharmaceuticals in 1991, and Infinity Pharmaceuticals in 2001. He was also founding editor of the journal Chemistry & Biology, which is now in its tenth year of publication.

What is your opinion on the recently announced NIH Roadmap?

For some time there has been discussion about funding trans-institutional science, but what is perhaps surprising to some people is how much emphasis the NIH Roadmap has placed on small molecules and screening in an academic environment. A meeting with some senior pharma industry executives made me realise that there are many people who are unhappy with this activity. When I went back and read what is being proposed, some of the language suggests that the plan is to fund early drug discovery and development in an academic environment. Yet some of the language also suggests that the Roadmap is about a parallel process of using chemistry and small-molecule synthesis and screening to interrogate biology. In this model, a parallel set of techniques is involved but the overall goals are very different. I am equally concerned as the pharma industry if the Roadmap were to place too much emphasis on the first model, because I think that a focus on drug discovery in academia would represent a missed opportunity.

Sending the message to groups of industry-naive biologists and chemists that they should now try to discover drugs in their lab could be problematic for a variety of reasons. It might be helpful for the whole scientific community to receive some clarity on the funding of chemical biology research in an academic setting. Is the main mission to promote early phase drug discovery in both academic and pharmaceutical environments? Or, is the primary intention to promote open sharing of reagents and data derived from chemical biology interrogations in an academic setting, as a parallel process to pharmaceutical industry research?

'A focus on drug discovery in academia would represent a missed opportunity'

Of those two options, I support the latter, and I'm concerned about the former. The former seems to be mixing up the strengths of the two environments. The pharma environment is focused on achieving the goal of developing safe and effective drugs. The academic world is well equipped to push the frontiers of synthesising new kinds of compounds to reach intractable targets, to develop both the computational science and informatics tools to allow efficient management of data and information and, most importantly, to develop assays that cut through a much wider swath of biology than is currently being achieved in the pharma industry. If you focus on developing drugs you must credential your drug target and allocate your resources accordingly. This doesn't allow for a blue-sky, high-risk exploratory undertaking that might reveal an unexpected drug target. The open-source, sharing model enables academic environments to use small molecules to come up with novel insights. It's not making a drug, but it's what the academic environment does well and it can have a dramatic effect on the overall drug discovery process. I think encouraging academic environments to move towards a more focused drug discovery element would be an ineffective use of resources.

Of course, the counter argument is that pharma will only develop drugs for large market diseases, leaving it up to academia to develop drugs for neglected diseases. This is an important consideration, but I don't think the open-source model will fail to fill this gap. If, in an academic setting,

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there are interrogation processes using small molecules that would point the way to small-market therapeutics, this will enable pharmaceutical groups or more focused biotech companies to go after those markets. I still think we'll be able to reach out to underrepresented diseases. (Dr Schreiber returns to this overall point towards the end of the interview.)

The Roadmap initiative promises to encourage the integration of different scientific disciplines. How did you personally come to work at the interface of chemistry and biology?

It was a slow process. I trained as a graduate student at Harvard University in the mid-1970s, in the midst of the controversy about whether recombinant DNA should be allowed and practiced in the university. At that time I felt that my topic of organic chemistry was so much more interesting and relevant to the ultimate understanding of life sciences. I was perfectly happy to have the attention drawn to the biology world because I didn't have to gloat that – in my narrow-minded view – I was clearly involved in the most interesting science! I was blind to what was going on in biology until I went out and established my own lab at Yale University. Early on in the process I began to understand why people were calling my field – the venerable field of organic chemistry – a more mature one. It became clear that to actually make discoveries in a very old and developed field was quite difficult, compared with the fertile field of biology and life sciences. That realisation came three years into my independent career, and so I began to teach myself biology and catch up on its wonders, and I haven't stopped since.

You've obviously managed to do that with great success but do you think it is difficult for a biologist to learn chemistry in the same way?

It is popular for chemists to say that biologists can't learn chemistry the way that chemists can learn biology. Let me try to refute that argument. When a chemist makes that statement, they are underestimating how difficult it is to learn biology. I've been studying biology for the past 20 years without any formal education and I still do not consider myself a true card-carrying biologist. There's something special that the great biologists have that enables them to see deeply into the fundamentals of biology. When I see that in them, I feel some jealousy. It's difficult to achieve that level of penetration without learning biology early in your training. It's a challenge to go in either direction and it's certainly the case that more people have moved from chemistry and physics to biology, so maybe there's some truth to the statement. But hidden in that statement is some sense that any chemist can move to study biology because biology is a rather simple subject – it is far from that. Biology is easy to learn superficially, but it's not easy to learn to the degree that you can make truly fundamental insights into its underlying principles.

'If you have architect's genes and love building beautiful buildings you'll be attracted to synthetic chemistry'

You have professed 'a love of synthetic chemistry', particularly of natural products. What first drew you to that science?

It was simply the aesthetics of these molecules – they are very beautiful art forms. And it was also the intellectual challenge of making them. If you have architect's genes and love building beautiful buildings you'll be attracted to synthetic chemistry.

When I was young and trying to think of what to do, the only thing I cared about was what would keep me fascinated. I wanted to make sure that I could do two things: be fascinated by whatever I did, and stay out of the Vietnam war, and I knew that going to college would increase the probability of the latter! The idea of making a living or having a successful career was a foreign concept. Then, three years into my independent career at Yale, I had my little epiphany about the wonders of biology. My fascination and love of building these molecules was really reinforced, but for a very different reason. I saw this as my avenue for entering into this fascinating world that would distinguish me from the biologists. I had this ability to make small molecules that otherwise resulted only from a billion years of biosynthetic tinkering and natural selection These compounds are highly effective at modulating biological systems, whether they be the natural hormones in our body, brain neurotransmitters, natural products produced by frog skin or plant leaves, or microbes in soil.

I knew this was my calling in life. I would make molecules that would perturb biological systems, with the idea that if you could observe the consequences you might gain some insights into them. I naively thought that this was a new idea, only to discover that it was a very old and well-known one! It is the essence of the genetic approach. Except geneticists don't perturb with small molecules, they perturb with mutations in genes. This is the explanation for the term chemical genetics. It's humbling that what I thought was a novel idea is, in fact, a very old one that is central to the way biologists had been thinking about biology for many decades.

In the mid-1990s, I realized that we needed to move away from the ad-hoc case-by-case application of small molecules to understand biological systems, although this method had been extraordinarily successful. There have been several Nobel Prize winners – Paul Greengard, Arvid Carlsson – whose work focused on powerfully illuminating compounds. In fact, one was a natural product – reserpine – which Arvid Carlsson studied, leading to the understanding of dopamine and neurotransmission in the brain. There are many examples, and my own lab got involved in some of them, for example by looking at FK506 and cyclosporin, which led to insights into the calcium–calcineurin–NFAT signalling pathways.

Later, however, I realised that there was a limitation in our so-called chemical genetics approach. If you happened to have a compound that had an interesting effect, then you might be able to study that property. But, if you wanted to study the basis of memory and cognition, for example, it wasn't so obvious what you would do next. The creation of ICCB came from recognising that to take the next step forward we needed to develop a set of techniques that would enable the systematic use of chemical genetics for any problem in biology, much like exists with genetics itself.

What do you think is the Holy Grail in natural product chemistry?

My answer is probably very different from a true natural product chemist. Personally, I would like to be able to bypass natural products altogether. That is, to develop an understanding of synthetic chemistry so that by linking synthetic chemistry to computational science you could sit down

with a piece of paper and design chemical pathways that would populate chemical space in a way that is meaningful to the biological or medical problem you are studying. Most natural product chemists would say that is hardly a Holy Grail for them because it would make natural product chemistry obsolete!

'Personally, I would like to be able to bypass natural products altogether.'

But here is a different view: There's a very interesting notion that the natural products of which we know might only be the tip of the iceberg. There are a vast number of microbial organisms that we are unable to culture under currently known conditions. However, one can extract the DNA from soil containing these organisms as single cell spores, some of which might have been resting dormant for many years. It's an exciting, and not just theoretical, possibility that we could reanimate the operon that controls the manufacture of natural products, which have not been produced by these organisms for possibly many decades or centuries, in a host microbe such as *Escherichia coli*.

Jon Clardy [Harvard Medical School] proved this concept with his work on environmental DNA (eDNA) while at Cornell University [4]. He took a scoop of soil and randomly cloned big chunks of DNA into bacterial artificial chromosomes, transformed *E. coli* and found transformants that made natural products that they did not normally manufacture. He then isolated and sequenced the DNA and realised that he had picked up a piece of DNA from an unknown dormant organism. The idea of reaching back in evolutionary time, through molecular methods and capturing the DNA that encoded compounds made eons ago is very exciting to me.

What is your laboratory working on at the moment?

There are three interconnected projects that fall under two general categories: chemical biology, and cell states and circuits. One project is in the chemical biology category and involves trying to push the frontiers of basic chemistry, such as diversity-oriented synthesis and the principles of chemical genetics, and involves a lot of technology development.

In trying to understand cell states and circuits, we divide this area into two different cell regions or processes: cytoplasmic and nuclear. On the cytoplasmic side we study signal transduction, but the particular problem we've homed in on is the nutrient-response signalling network. I see this as being central to metabolic diseases such as diabetes and cancer. On the nuclear side, we are studying chromatin, which was initiated by our discovery of the first histone deacetylase in 1996 [5]. Recently we've discovered that the principles that underlie the circuitry of chromatin appear to be very similar to those that underlie signalling in the cytoplasm. This contrasts to what had been a commonly stated view of chromatin as a histone code.

The tie-in with the chemical biology program is that we can create signatures of cell states through the use of small molecules and screening processes. A cell's response to perturbagens can create signatures similar to those provided by expression profiling. The chemical biology program provides the signatures that equate with cell states – this presents a challenge in pattern recognition. We believe that the circuitry that underlies chromatin is similar to that which underlies cytoplasmic signal transduction, and we came to this conclusion by solving a problem in causality recognition. Pattern recognition comes first and is facilitated by the use of chemical biology, but causality recognition is the Holy Grail for understanding the circuits that underlie biological systems. It is an even greater challenge.

Does your laboratory's work on cell states and circuits constitute a move towards systems biology?

Harvard University and Massachusetts Institute for Technology (MIT) recently announced the creation of a jointly held institute called the Broad Institute (http://www.broad.mit.edu), named after Eli and Edythe Broad, the philanthropists who made an initial donation to make the Institute possible. The Broad Institute's two founding assets are Harvard's ICCB and MIT's Genome Center [directed by Eric Lander, also now Director of the Broad Institute]. I currently have laboratories in three locations, one in Harvard Square, one at the Harvard Medical School, and a third lab that is part of the Whitehead Genome Center, which is where we create and study these cell state signatures. Once the Broad Institute building is opened my intention is to consolidate these labs and to enable them to be more associated with our neighbouring scientific community. From there we will conduct research in various metabolic diseases, cancer biology, cell states and circuits, and psychiatric disease. However, this is not what most people think of as systems biology – we think of it as extending genomic principles to medicine.

Harvard recently started a new systems biology department led by Marc Kirschner. Marc and his colleagues view systems biology as resulting from cell biologists and developmental biologists getting together with mathematicians and theorists to create computational models of cells and tissues and organisms. This is an exciting and ambitious undertaking – ambitious especially if we're still in the components stage, and we still have to characterise all of the components. I suspect that we need a great deal more work in the area of identifying cell components, states and circuits. We all agree that we need to able to use the power of mathematics and computational science to understand, in a truly robust way, how cells, tissues and organisms function.

What are the objectives behind Chembank and the Initiative for Chemical Genetics?

The ICG is a contract with the National Cancer Institute (administered through SAIC), and it funds the infrastructure that we've built at ICCB to enable chemical genetics to be performed. ICCB is becoming a national laboratory for small-molecule screening. We have provided screening services for over 80 laboratories nationwide – including the chemistry, screening and informatics technology – and to make that widely available we need the help of professional staff, made possible by the ICG. Otherwise the ICCB would have been a local activity that supports only a limited number of laboratories in this area.

Chembank comprises informatic tools and linked databases that enable the use of small molecules to interrogate biology and medicine widely and effectively. It enables Internet users to access a staggering amount of information from small-molecule screening and, ultimately, decipher it and improve our knowledge and understanding of these systems. We have a central repository of information that we want to make available to the scientific community to enable the sharing

of this information. ICCB's primary mission is to share data and reagents derived from small molecule studies of disease biology – we are able to pursue this mission because we're not directly involved in drug discovery.

You once mentioned that you had a goal of a small-molecule partner for every gene in the human genome. Does that still stand?
Not only does it still stand, it has been refined. When I first said this at a meeting in Kyoto nearly ten years ago, it was in part to make a simple statement that one could grasp immediately, akin to "sequence every gene in the human genome". But technically speaking, that challenge understates what we really want to do, which is to use small molecules to modulate the individual function of multifunctional proteins, activating or inactivating individual functions as necessary. This is one of the differences between small molecules, for example, and the knockout or knockdown technologies, where you inactivate everything to do with the protein of interest. Small molecules allow you to gain control rapidly, and can be delivered simply but, most importantly, we've shown that we can discover molecules that only modulate one of several functions of a single protein (for example, see refs [6,7]). So, the new statement should be 'a small-molecule modulator for each individual function of all proteins'. It's a big challenge: there are probably 5000 such small molecules out there right now, and there could easily be 100,000 proteins and 500,000 individual functions. So we've identified 5000 out of the required 500,000 small molecules, which is similar to where the Human Genome Project was in year two of its 12-year journey. That might be a useful calibration – optimistically we're ten years away. I think it may happen and if it does the impact on drug discovery is going to be enormous because the earliest part of the drug discovery process could be bypassed. The hard part will still exist, in preclinical and clinical development, but it will be the hard part of a problem that we wouldn't even have tried to tackle today. The knowledge that you can modulate a particular pathway is more important than the knowledge of which compound will be the best drug. Developing and sharing this knowledge is the domain of academic research. Finding the best drug will still be challenging, but if you know you can accomplish it then you can marshal the resources needed to achieve that goal, as the pharmaceutical industry has shown over and over. But this is the domain of the pharmaceutical industry – that's where the actual drug development should take place in my opinion.

'The idea of a limited number of targets is nonsense'

It has been said that drug discovery is getting harder and productivity is reduced because we have already exploited the 'low-hanging fruit' targets. What is your take on this?
The idea of a limited number of targets is nonsense. My prediction is that we're going to discover a whole bevy of new targets that we currently view as simple housekeeping proteins. One example is the heat shock protein, hsp90, which has long been regarded as having a housekeeping function and which exists in the vast majority of cells as an isolated protein. The natural product geldanamycin, a derivative of which is being tested as a cancer therapeutic, binds to hsp90 very weakly. However, when a cell is stressed, including the stress associated with transformation towards cancer, hsp90 moves into a multiprotein complex that is essential for the viability of the cancer cells and, amazingly, the geldanamycin derivative binds to the multicomponent complex with subnanomolar affinity [8].

To me, one of the major new insights from biology in the past five years is that proteins we thought had routine functions in metabolism are now being shown to have specific effects in cancer and metabolic diseases. Circadian rhythm also turns out to be regulated by proteins that have a housekeeping function but are then recruited to more specialised functions, creating a new microenvironment for that protein and rendering it a potential therapeutic target. Of the 100,000 proteins in the proteome, my guess is that a substantial number of them will yield a therapeutic benefit, should you be able to modulate their therapeutic function with a small molecule.

Your research focus has been mostly looking at proteins, but what progress in the study of nucleic acids have you found exciting?
With respect to small molecules, RNA is an area where progress has been slow but is now promising. It is clear that RNAs have structures that in certain respects are more reminiscent of protein than of DNA, and accordingly there are several small molecules including natural products, such as erythromycin, that specifically target RNA. Given the feasibility of targeting specific RNA structures with small molecules, and given the seemingly never-ending set of new discoveries regarding functions of RNA, RNA molecules encoded by the genome – such as the natural gene-silencing miRNA molecules – are theoretically now targets for small-molecule drugs. It's an exciting frontier, but still a very challenging one because it is currently difficult to achieve the kind of specificity that you can achieve with small molecules that bind to proteins.

We mentioned earlier about intractable targets, are there any innovations in chemistry that could impact on these targets?
You can consider intractable targets in two ways. There are medically relevant targets that have proved challenging to target with small molecules, such as presenilin and some of the tyrosine phosphatases. But there's also a general problem with selectively disrupting protein–protein interactions. If successful modulation of interactions could be achieved, it could have a big impact on drug discovery. Admittedly, I am biased, but I think one technology that could crack this problem is diversity-oriented synthesis, by creating more complex molecular contours that are potentially more relevant to the topographic problem of disrupting protein–protein interactions.

Has progress in protein microarray technology impacted your work?
To some degree it has. One of the first protein microarrays was actually made in my lab by Gavin MacBeath, who's now a faculty member of my department. Personally, I have not been involved in development of the technology – in part because within my own department we have one of the world's experts – but I'm really quite excited to see how the field develops. I think the impact is going to be substantial, and I would like to collaborate with Gavin MacBeath and others in this field. We have a paper that has been submitted with Mike Snyder from Yale University, where we used his protein

microarrays to identify the protein target of a small-molecule modulator, so this is one of many examples of the potential uses of protein microarrays in our work.

'The winner is whoever makes the best drug'

If we imagine a future where pathways might be part of company intellectual property portfolios, in a similar way to Ariad's position with the NF-κB pathway, for example, how do you feel this would affect innovation in drug discovery?
I'm not an expert on this and don't follow it carefully. Also, it's a fact that I own stock in Ariad, so I am conflicted. However, I am concerned about this; it doesn't feel right to me. I have always believed in maximising freedom to operate and in the level playing field model of drug discovery. The bar should be lowered for people to operate in any intellectual environment they wish. The winner is whoever makes the best drug.

Who has been your greatest inspiration?
Muhammed Ali, Neal Cassady, and my dad.

What would you most like to have achieved by the end of your career?
To have contributed to the revitalization of chemistry, via chemical biology, as an integral component of the life sciences.

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