DDT Vol. 9, No. 18 September 2004

Stephen Neidle on cancer therapy and G-quadruplex inhibitors

Interview by Joanna De Souza

Stephen Neidle, Professor of Chemical Biology, The School of Pharmacy, University of London

Stephen Neidle was educated at Imperial College, London, where he graduated in chemistry and then proceeded to do a PhD in crystallography. After a period as an ICI Fellow, he joined the Biophysics Department at King's College, which ignited his interest in nucleic acid structural studies. He was appointed as one of the first Cancer Research Campaign Career Development Awardees, becoming a Life Fellow on moving to the Institute of Cancer Research.

He was appointed to the Chair of Biophysics at the Institute of Cancer Research in 1990, and moved to the new Chair of Chemical Biology at the School of Pharmacy in the University of London in 2002, where he also directs the Cancer Research UK Biomolecular Structure Group. He is currently Chairman of the Chemical Biology Forum of the Royal Society of Chemistry, which is involved in developing the interface between chemistry and the life sciences. He will shortly assume the Directorship of the newly-established Centre for Cancer Medicines at the School.

Stephen Neidle has received several awards for his work on drug–nucleic acid recognition and drug design, including the 2000 prize of the Biological and Medicinal Chemistry Sector of the Royal Society of Chemistry, and its 2002 Interdisciplinary Award. He was the 2004 Paul Ehrlich Lecturer of the French Societé de Chimie Therapeutique, and was recently awarded the 2004 Aventis Prize in Medicinal Chemistry.

Can you tell me a bit about yourself and your career so far?

I've been at the School of Pharmacy, University of London for almost 2 years as Professor of Chemical Biology. Before that, I worked for 17 years at the Institute of Cancer Research where, besides being Professor of Biophysics for 12 years, I undertook a variety of administrative roles, including being Dean of the Institute for 5 years until the time I left. One of the principal reasons why I moved to the School of Pharmacy is because I wanted to work in an academic medicinal chemistry environment that also has a strong commitment to cancer research.

How did you eventually come to work at the forefront of such research?

I originally trained as a chemist and a crystallographer. I developed an interest in biological molecules, particularly nucleic acids, when I worked in the Department of Biophysics at Kings College. From that point, my work focussed on the interaction of small molecules with nucleic acids. Essentially all that work, from then until now, has been continually supported by Cancer Research UK. Nowadays, my lab has a multi-disciplinary environment, with chemistry, some cell and molecular biology, molecular modelling, crystallography and drug design. We were actually one of the first academic laboratories in the UK, certainly in the cancer area, to get into computer-aided drug design. We are a little bit like a small biotech company in that we do much of the chemistry here within the Group, as well as associated cell and molecular biology. It's very much an integrated effort and typically people who work here are trained in several skills, and that's very much encouraged.

Can you tell me about the current research in your laboratory?

Most of our effort is in the area of cancer chemotherapy, in particular the discovery of new agents against one specific category of target, telomerase and telomere maintenance. Telomerase is the enzyme that maintains the integrity of the ends of chromosomes in tumour cells yet is not activated in normal somatic cells. In conjunction with an industrial partner, we are working towards taking our molecules through to the development of potential clinical agents and we're very excited about this because the clinical agent that is now on the horizon as a reality, is based on simple, scientific concepts that we were involved in devising several years ago.

'The clinical agent that is now on the horizon as a reality is based on simple, basic science concepts.'

What made you focus on studies of telomeric DNA, the design of G-quadruplex inhibitors and sequence-specific DNA recognition?

Well I guess that part of the reason is because for years my colleagues and I have developed a large knowledge base and understanding about the structural principles underlying small-molecule interactions with nucleic acids and it was a logical move to then develop the idea of looking at molecules capable of interacting with higher-level organized DNA, such as quadruplex DNA. There was always the possibility that this could be very different from interacting with normal genomic DNA and so I think right from the outset we saw the possibility that this could be selective - that concept is still with us. Also the biology of telomerase and telomeres is currently being developed worldwide and it's by no means a mature area yet; it's still a very exciting field and one that is amenable to novel therapeutic approaches

What evidence has driven you to believe that knowledge about the molecular structures of nucleic acids and their complexes can be applied to novel small-molecule inhibitors, so that they can possibly be used as selective anticancer agents?

First of all, in the quadruplex area, without this knowledge we simply would not have been able to develop such small molecules. It's very gratifying that an increasing number of laboratories around the world have taken up the quadruplex-ligand concept and are developing novel types of

 PII: S1359-6446(04)03214-3

molecules. We also have interests in the area of sequence-specific duplex DNA recognition, in particular a long-term collaboration with Professor David Thurston and his group at the School of Pharmacy. The work of most people in this area, as well as our own efforts, has been based on the understanding of the double helical structure of DNA. So without structural concepts, none of this field would have developed and leaders in this field, such as Dervan at Caltech, and others, have also based their ideas for ligand design ultimately on structural principles.

'…drug discovery in the cancer area… tends to be the slave of fashion.'

It has been said that drug discovery is getting harder because of intractable targets. How do you feel about this comment and what sort of impact has it had on your work?

I think drug discovery is getting difficult for a variety of reasons, but it's not difficult for everybody in the same way. One of the problems is that drug discovery in the cancer area (and I can only really speak with knowledge about this area, although I suspect that to some extent these issues apply to others) tends to be the slave of fashion. High-throughput screening, which is just now starting to fall out of fashion, itself followed on from the dogma that everything could be done by structure-based design. Some thought should have made people realise that the reality of drug discovery is always going to be more complex than what can be achieved by reliance on a single methodology. Also in the cancer area, I think drug discovery seems to be harder because of the optimism that was generated by the idea that the great deal of knowledge about cancer pathways and individual oncogenic proteins, which we now have, would automatically lead to new therapeutics. Cancer is too complex a disease for that simplistic approach. It's hard because expectations were perhaps over-optimistic. We see this in specific disease or target areas, such as kinases, where only the exceptional such as the Bcr–Abl target in CML [chronic myeloid leukaemia] has emerged as a clinically viable target that has resulted in significant therapeutic outcomes.

I think we also have to take onboard the issue that the driving force behind drug discovery has changed from a traditional chemical to a biological one. Unfortunately, I think that many of our biological colleagues have a slightly naïve view of what chemistry can do. To a large extent, they think it's handle-turning, and that chemistry is simply the slave of those who derive the targets. Perhaps that's why the over-reliance on high-throughput screening was always bound to fail, and why the pipeline of clinical agents in so meagre. The reality is of course that chemical space is far larger than we can ever probe by using high-throughput screening. Much more than it is at present, chemistry needs to be a key partner in the drug discovery process; chemical intuition and an understanding of chemical mechanisms, chemical pathways, uptake and metabolism are needed and not just chemical synthesis.

'Far more then it is at present, chemistry needs to be a key partner in the drug discovery process.'

How far do you believe that cancer is a caused by a person's environment and lifestyle? What do you believe is the main cause of cancer?

I tend to be one of those annoying people who answers that sort of question on the basis of evidence, not so much from belief. It's very easy and equally true to say what we all know – that the single major causative agent in human cancer is tobacco. Beyond that I think that it's awfully difficult to pinpoint causative agents that aren't obvious and it's therefore very important that we continue to encourage epidemiology and molecular epidemiology to answer those questions. If you look at the statistics of the common solid human tumours in the UK, you will often see a rise in their apparent incidence, but you've got to take out from that the factors of improved earlier diagnosis and the fact that the population is living longer. Cancer is a disease of old age – that much we do know.

What do you think is currently the most effective form of treating cancer?

The single most effective form with early diagnosis is undoubtedly surgery. We sometimes forget that. If you can get to a cancer early enough then surgery can be very successful.

Do you see potential benefits from your research in other therapeutic areas, such as aging?

It's undoubtedly true that when the excitement of telomeres and telomerase first reached its peak in the mid-1990s, it was felt that this was an important factor in the immortality of humans. It's clear that telomerase plays an important role in the immortality of cancer cells, but I think it's probably simplistic to believe that human aging and the lack of immortalisation is solely due to telomere maintenance or the lack of it. Like many areas of biology, the reality is far more complex and we just don't understand it as yet.

We also have an interest in sequence-specific DNA recognition and we have recently been looking at the potential of these molecules as antibacterial reagents, particularly against resistant strains such as MRSA. These molecules have great potential – and we are not the only people to have realized this – probably by virtue of their excellent pharmacological properties.

'Academics can't compete head-on with biotechs and nor should they.'

How do you see your research developing in the future? What would be your next major target?

Well we're still very much involved with the telomerase area and we look forward to some of our molecules getting into the clinic within a reasonable time frame. If we do see positive clinical effects then we will be looking at moving to develop second-generation molecules, but that's going to take a lot of time and effort. Beyond that, we're looking at a range of other potential targets. I think it's always very important in an academic environment not to try to be a biotech or pharma company. I said we're like a biotech, but only in some ways. Academics can't compete head-on with biotechs and nor should they; our approaches should be different, if not orthogonal. I believe there is an important role for academics, in drug discovery, particularly in cancer. We have the ability to take insights and new discoveries in a very flexible way and find novel inhibitors

from mechanism-based approaches in a way that's not always possible in industry (if we can get funding!).

What have been the particular difficulties associated with the quadruplex approach? (for example, compound potency, physical properties, delivery, metabolism, toxicity?)
The principal difficulty has been convincing many of our colleagues that the approach was viable and demonstrating that it was actually valid. Aside from that, when going from an inhibitor to a potentially real drug, I'm very aware of the need to take all those factors you mentioned into account, and I think that's why a broader chemical-based view is so important. One of the critiques of high-throughput screening is that you have to bolt on at the far end all these important points about delivery, uptake, metabolism and so on, and incorporating them at the outset is far more difficult. We're trying to do that as an integral part of the design and discovery process. We're trying to do it intelligently, in an evidence-based way, accumulating experimental data as we go along.

Could you outline the particular advantages of this approach over other potential telomerase-based molecular therapeutics?
One of the apparent inherent problems with telomerase inhibition is this: human telomeres are always relatively long, typically in cancer cells, several thousand bases in length. In normal cells, they're typically considerably longer. What happens in normal cells (because there's no factor such as telomerase to stop this occuring) is that each round of replication doesn't fully replicate the ends of chromosomes, so they become shortened after each round. Lets say a telomere is 5000 bases long, every time you replicate you might be losing 200 bases, so after 25 generations, the cell will get to a point where its telomeres are critically short, and the cell then responds by going into a non-replicating phase, termed senescence, which it can't easily get out of. Typically a cell will then move on to apoptosis. So, in other words, normal somatic cells have a defined lifespan (hence the interest with telomeres and aging). By contrast, cancer cells have this activity, telomerase, which is a reverse transcriptase that is able to both replicate and synthesize further telomeric DNA nucleotides in synchrony. So the net effect is a stabilization of telomere length and those cells are immortal as a consequence.

Now, if one uses a catalytic inhibitor to stop the telomerase from doing this then you have to wait 20 generations, or whatever the exact number is, before senescence and cell death with the cell eventually behaving as a normal cell. It wouldn't be a viable form of therapy because you'd have to wait these 20 or so generations, perhaps more, and during that time, in a cancer context, a tumour could grow (and tumours can grow very rapidly) and overwhelm the host before the therapy was effective. So it was that realization, I guess, that was one of the big 'downers' on this field as it dampened the enthusiasm of telomerase as a good target. I'm not sure that we fully realized this at the outset – although we realized pretty quickly once we had the experimental data– that actually targeting not telomerase *per se*, but its substrate, telomeres, overcomes that problem. This is the critical advantage, I think, of the G-quadruplex approach in that it induces rapid effects. So, typically in a human tumour cell line, or in a tumour-bearing animal, one sees effects within 5–7 days, sometimes less. And that's because the induction of a quadruplex type of arrangement at the end of telomeres stops not only telomerase from functioning catalytically, but it disrupts the ends of telomeres in cancer cells altogether and they become non-viable very quickly.

'…a quadruplex type of arrangement at the end of telomeres stops not only telomerase from functioning catalytically, but it disrupts the ends of telomeres altogether.'

Are clinical trials of these compounds rendered more difficult as treatment of the cancer cells might not be immediately cytostatic or cytotoxic?
We actually envisage that clinical trials would not be more challenging than normal because these molecules are acting rapidly at least in cell-based experiments. This is also the experience seen to date in xenograft experiments. There is no time lag with these molecules as one might've expected and as one sees with other types of telomerase inhibition.

Do you envisage these molecules being administered as monotherapy? Or would they be more effective as an adjunct?
We see no reason why they may not be administered as single agents. We've also done some cell-based studies with these agents and cell-cycle inhibitors and we see synergistic effects so we're confident that we will be able to explore, in due course, the potential for drug synergy.

Can you tell me a bit about the collaborations that you are working on at present?
Well, in this particular area we have collaboration with a UK-based biotech company called Antisoma. It's a very fruitful collaboration because it's a synergistic one; they have skills and expertise that we don't have, especially in preclinical pharmacology and in setting up clinical trials, and they also bring to us the skills that academics don't have in project management and moving projects to a preclinical point. I have also been able to re-establish a very fruitful collaboration with Professor Lloyd Kelland, Antisoma's Head of Laboratory, which started when we were both at the Institute of Cancer Research.

I also have a very good collaboration in the quadruplex field with an excellent young chemical biologist in Cambridge, Shankar Balasubramanian. We like to collaborate with a broad range of people, from the chemical, biological and clinical sides, so we have an extensive range of international colleagues.

In your opinion, who is doing really exciting, innovative research at present?
Well, it's always difficult to single out individuals, but I think Shankar in Cambridge is a very bright scientist who has interests that are based on an excellent understanding of the fundamental mechanisms of polymerase action, and who personifies the type of approach and thinking that is needed at the chemistry–biology interface. In the UK DNA damage field, Steve Jackson is exceptional but in the cancer chemotherapy field in the UK we've got disappointingly few people who can generate new chemical agents and create drugs, which is a real problem for the future, and one that the major funding bodies have not addressed. There are just a couple of major players, who've had profound influences on that field – Malcolm Stevens at Nottingham stands out

on the world stage. Although younger, David Thurston at the School of Pharmacy here, is achieving much. Looking slightly further afield in the quadruplex area, Laurence Hurley in Arizona [The University of Arizona Cancer Center] is a very major player, again at the chemistry–biology boundary.

'I think that the excitement of science is that one cannot predict breakthroughs.'

What do you envisage as being the next big 'breakthrough' in your field of work?
If I knew that I would've done it already! I think that the excitement of science is that one cannot predict breakthroughs. It's absolutely the opposite; you can't. If one didn't have that edge of excitement then it wouldn't be a field that attracted so many exceptional people.

Who or what has been the greatest influence in your career?
When I was an undergraduate, one member of the department I was in at Imperial College was undoubtedly one of the major figures in 20th century chemistry – Derek Barton. I got from him the realisation that 3D structure is the key to understanding both chemical and biological behaviour. This has been a major driving force on my science in many ways, together with the view that chemical intuition generally is very important in understanding and exploiting biological processes.

What do you think is your greatest career achievement to date?
There are two answers to that question. One is contributing to a body of information about the way that small molecules interact with nucleic acids in the broad sense and helping to ensure that this information gets translated into the design of potential therapeutic agents. The other is more specific in that I am fortunate to be playing a leading role in the development of quadruplex inhibitors of telomerase, right from the outset.

What would you like to have accomplished by the end of your career?
I want to see some of our molecules in the clinic treating human cancer effectively; I hope that I will see that.

Stephen Neidle
Professor of Chemical Biology
University of London School of Pharmacy
29–39 Brunswick Square
London, UK WC1N 1AX

The *Discussion Forum* provides a medium for airing your views on any issues related to the pharmaceutical industry and obtaining feedback and discussion on these views from others in the field. You can discuss issues that get you hot under the collar, practical problems at the bench, recently published literature, or just something bizarre or humorous that you wish to share. Publication of letters in this section is subject to editorial discretion and company-promotional letters will be rejected immediately. Furthermore, the views provided are those of the authors and are not intended to represent the views of the companies they work for. Moreover, these views do not reflect those of Elsevier, *Drug Discovery Today* or its editorial team. Please submit all letters to Steve Carney, Editor, *Drug Discovery Today*, e-mail: S.Carney@elsevier.com

Therapeutic control of free radicals

In a recent issue of *Drug Discovery Today*, Brian Day reviews the status of one promising approach to the problem of therapeutic control of free radical production: the creation of drugs that mimic the activity of superoxide dismutase (SOD) [1].

The past 35 years have witnessed the delineation of a remarkable number of roles for the superoxide radical and related metabolites in human diseases, as well as in the regulatory and signaling processes of healthy cells. From the beginning, there have been attempts to restore normal oxidative balance by the therapeutic application of SOD, the body's own radical-scavenging enzyme, in one form or another. Many of these attempts have been awkward or flawed, but much has been learned in the process. Although success has often been dramatic in laboratory models, to date there has been no real success in translation to human clinical medicine; perhaps that will soon change.

One major problem has been that enzymes generally make poor drugs. They are expensive to produce, sometimes immunogenic and often quickly cleared by the kidneys. Because they are large molecules they do not gain access to compartments inside cells, and sometimes have trouble even with extravasation to tissue interstices. The SOD-mimetics reviewed by Day offer possible solutions to these problems. The mimetics differ from SOD in another important way that could be advantageous or not, depending on the application. Enzymes have great (if not absolute) specificity, whereas the mimetics generally catalyze a variety of redox reactions *in vivo*, the extent of which might never be known. Although some of these reactions might be fortuitous (e.g. the catalase-like elimination of H_2O_2), others might be detrimental (e.g. the oxidation of NADPH). Thus, the potential toxicity of the mimetics can present a new set of problems.

1359-6446/04/$ – see front matter PII: S1359-6446(04)03211-8