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.

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**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.

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An obstacle faced by both mimetics and enzymes is the unfortunate sharp bell-shaped dose-response curves seen when SOD activity is used to inhibit many superoxide-mediated phenomen,a such as reperfusion injury [2]. The behavior appears to be due to the ability of superoxide to initiate the chain reaction of lipid peroxidation and, paradoxically, to terminate the same process. Accordingly, a single optimal concentration of SOD activity exists for any pathological situation, reflecting a compromise that limits initiation events while still allowing significant termination to take place. The concentration of SOD activity is critical only while substantial lipid peroxidation occurs. Healthy cells can tolerate a range of SOD concentrations with few ill effects, but whether they fare better [3] or worse [4] when challenged by oxidative stress depends on precisely how much SOD is expressed, as seen in studies of transgenic mice exposed to ischemia/reperfusion. More is not always better, and sharp bell-shaped dose response curves are a pharmacological nightmare.

The questions of where superoxide is overproduced in a particular disease state and whether the SOD or mimetic has access to that location lead one to speculate that we might ultimately need a variety of SOD-like drugs with properties tailored to specific applications. In inflammatory diseases, the primary sources of superoxide production are activated neutrophils, resulting in free radical attack from outside the cell; in diseases of ischemia and reperfusion injury the superoxide is largely generated by mitochondria within the cell. Thus, it could be that enzymes are best suited for anti-inflammatory applications [5], whereas the mimetics, with access to the mitochondria, might be best suited for the treatment of reperfusion injury [6].

A third approach that has received little attention is drugs that can upregulate the body's production of its own antioxidant enzymes.

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## Drug discovery in the HIF pathway: where do we go now?

In the USA nearly two-thirds of all deaths are attributed towards heart disease, cancer, cerebrovascular disease and chronic lung disease. Reduced oxygen levels (hypoxia) and deregulation of HIF, a hypoxia responsive transcription factor, have been shown to constitute a major component of these disease states [1]. Tremendous advances over the past few years have uncovered a family of hydroxylase enzymes at the centre of HIF regulation. This family of enzymes adds oxygen to key amino acid residues in HIF, playing an important role in sensing oxygen levels and regulating the activity of the HIF proteins [2].

In a recent article in *Drug Discovery Today*, Hewitson and Schofield [3] provide a timely review outlining our current understanding of the regulation of HIF by the HIF hydroxylases. The authors provide a balanced analysis of the opportunities and possible limitations facing the pharmaceutical industry wishing to develop therapeutic interventions for HIF.

Selecting the most appropriate point of the HIF pathway to target for drug development will be vitally important for achieving a successful clinical outcome. One would initially assume that the HIF hydroxylase enzymes would be that appropriate target. Hewitson and Schofield [3] suggest that targeting solely the HIF hydroxylase enzymes might prove technically difficult, essentially due to the similarity of the enzyme's active site with other known hydroxylase enzymes, such as those involved in collagen biosynthesis and DNA repair.

Instead, they suggest that it could be more advantageous to target the substrate-binding site located within the HIF protein. However, the disruption of protein–protein interactions has not been generally thought of as a suitable molecular target for drug development by the pharmaceutical industry. The reasoning behind this has been that small molecules are less likely to be effective in disrupting complex interactions between two proteins, which normally occurs over numerous interfaces, unlike inhibiting an enzyme by occupying its enzymatic site. In the current era of HTS this might no longer be a dilemma. For example, recent small-molecule inhibitors that successfully target the dimerization interface of the MYC and MAX transcription factor proteins have been discovered using HTS [4].

Over the past few years, the rapid progress made in understanding the


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