Journal of
Medicinal
Chemistry

Volume 48, Number 2 January 27, 2005

2004 American Chemical Society Award for Computers in Chemical and Pharmaceutical Research

From Diatomics to Drugs and Distributions

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Received July 20, 2004

Introduction

It may seem to be overdoing things to go back to one's birthdate when giving a retrospective. Mine, however, was significant: October 1, 1939. It meant that I missed compulsory military service by 1 day, have a year's extra salary over and above what I would have if born 1 day earlier, and of most relevance, became a graduate student in 1961. This last fact meant that I was one of the first generation of graduate students to use a computer. I joined the research group of Richard Barrow to work on experimental diatomic molecule spectroscopy but stumbled into the application of computers. Like so many careers, mine illustrates the cock-up theory of history rather than conspiracy. Working with a 32K Ferranti Mercury computer, pre-FORTRAN, did not seem an obvious entree into the world of drug discovery.

Diatomics

Trying to understand why the diatomic halogens hold together without dissociating longer than one might expect led me to try to calculate their potential curves from spectroscopic data using the Rydberg−Klein−Rees method.[1] Being lazy, I tried to write a computer program to do this, which led to the introduction of a correction to the theory but more importantly to the realization that with a computer any integral can be evaluated using numerical methods.[2]

Having been able to calculate the potential curves from experimental data, the notion of computing them ab initio using quantum mechanics seems an obvious next step and took me to Paris as a postdoctoral researcher with Carl Moser to learn those techniques. The spectroscopic background provided some good problems to pose for quantum chemical investigation. Together with Georges Verhaegen we did the first open-shell calculations to compute excited states rather than using virtual orbitals and applied this to clarify the electronic energy levels of BeO and its congeners, the experiments being inconclusive.[3]

On the return to Oxford, a similar problem opened up a rich vein of possibilities. This concerned the nature of the excited electronic state of BeF. The ground-state configuration is

$$^2\Sigma^+ \qquad 1\sigma^2 2\sigma^2 3\sigma^2 4\sigma^2 1\pi^4 5\sigma$$

but the first excited state could be

$$^2\Pi_r \qquad 1\sigma^2 2\sigma^2 3\sigma^2 4\sigma^2 1\pi^4 2\pi$$

or

$$^2\Pi_i \qquad 1\sigma^2 2\sigma^2 3\sigma^2 4\sigma^2 1\pi^3 5\sigma^2$$

In the $^2\Pi_r$ case the π shell is less than half-filled and the spin−orbit coupling constant should be positive, while if it were $^2\Pi_i$, then the more than half-filled π shell should lead to a negative spin−orbit coupling constant. The difficulty we found was that the energy calculation clearly shows a $^2\Pi_r$ state[4] but the observed spin−orbit coupling constant is negative. This dilemma forced us to attempt to calculate spin−orbit coupling constants from ab initio wave functions using perturbation theory.[5] The results were impressive as Table 1 indicates.

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10.1021/jm040136y CCC: $30.25
Published on Web 12/10/2004

Table 1. Spin−Orbit Coupling Constants

	calculated (cm^{-1})	observed (cm^{-1})
BeH	2.3	2.14
CH	30.4	28.0
OH	141.4	139.7
SH	362.0	382.4

Table 2. Off-Diagonal Spin−Orbit Coupling

	splitting in CH (MHz)
terrestrial experiment	3374 ± 20
astronomical experiment	3335.47 ± 0.01
calculation	3311

Pursuing the BeF problem further caused us to attempt to compute off-diagonal matrix elements of the spin−orbit coupling operator to calculate the tiny so-called Λ-doubling splittings, p and q:

$$p = 4\sum \frac{\langle {}^2\Pi|H_{so}|{}^2\Sigma\rangle\langle {}^2\Pi|B(L^+ + L^-)|{}^2\Sigma\rangle}{E_\pi - E_\Sigma}$$

and

$$q = 2\sum \frac{\langle {}^2\Pi|B(L^+ + L^-)|{}^2\Sigma\rangle^2}{E_\pi - E_\Sigma}$$

These calculations[6] proved to be a triumph for theory, enabling us to predict where radioastronomers should look in frequency terms for the species CH in interstellar space, which had long been predicted but never found. Our calculations proved to be more accurate than terrestrial experiment,[7] as Table 2 shows. This very respectable work might have continued for years, but an out of the blue event changed the course of my research toward the work of medicinal chemistry.

Drugs

In 1968 I received a letter from Anthony Roe of Smith Kline and French in Welwyn, U.K., enclosing a paper by Monty Kier[8] in which inevitably crude calculations on histamine suggested that it could exist in two conformations and hypothesizing that one conformer might bind to the H1 receptor while the other activated the H2 receptor. I had been sent the paper to evaluate because the group, headed by Jim Black (now Sir James Black) and Robin Ganellin, was working on H2 antagonists and needed someone who knew about wave mechanics to evaluate the paper. My quick response was that the idea was interesting but that there was no logical connection between conformers and binding sites, since histamine also exists in two ionic forms and also in alternative tautomers.

This discussion grew into a consultancy, and the SKF chemists made a series of methyl-substituted histamines and measured the relative H1/H2 potency, while we calculated the population ratio.[9] If the hypothesis were correct, then the potency ratio should correlate with the population ratio. It did not, but one important outcome of this, in which I did not play a part, was the finding that 4-methylhistamine is an H2 agonist but inactive against the H1 receptor (Figure 1): the role of the all-important methyl in the imidiazole ring of cimetidine was the final spectacular outcome of that

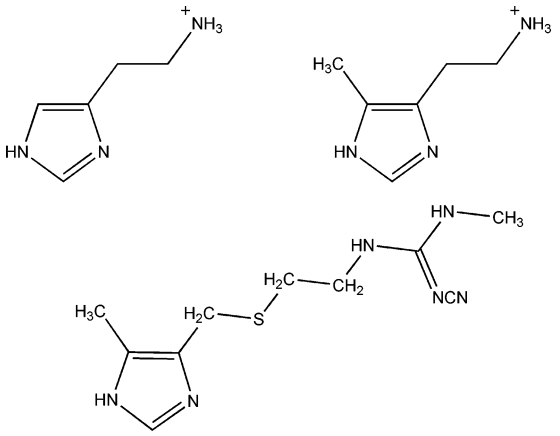

Figure 1. Histamine, 4-methylhistamine, and cimetidine.

research and that, along with his β-blocker work, resulted in the Nobel Prize for Jim Black.

Trying to explain why these small structural changes influence activity caused us to compare the possible shapes that different members of the series can adopt and the concept of the "essential confirmation" for activity, this being a nonequilibrium shape, which was a novel idea at the time.[10] Aspects of this were picked up and developed into CoMFA by Dick Cramer, then at SKF. That research also changed the direction of my own group, making me one of the first to apply theoretical chemistry to drug research, thought by many at the time to be a little dotty. In fact, in my 1976 book, *Quantum Pharmacology*, I questioned in the preface as to whether the title needed a question mark.[11]

After those initial steps the story of applying computers and theory to drug discovery was directly linked to developments in computer hardware and later software. One of my own steps was to produce the first colored computer graphics images of electron density and electrostatic potentials (Figure 2). These were made using a black and white screen and then photographing parts of the image through colored filters and winding back the film.[12] Both color graphics and in particular workstations took this type of work into the pharmaceutical industry in the early 1980s.

My own major contribution in that era was to highlight, modify, and popularize the concept of molecular similarity. We used the formulation introduced by Carbo[13] and an alternative with some minor advantages developed by my student Edward Hodgkin in his thesis. He and another of my students, Andy Good,[14] also introduced the use of Gaussian functions so that calculations of molecular similarity in terms of both shape[15] and electrostatic potential became quick and reliable using software we developed in the group. We also introduced a measure of the shape similarity between enantiomers, which gives a quantitative version of Pfeiffer's Rule which predicts the relative potency of mirror image forms.[16]

By the later years of the 1980s, computer power had become sufficiently available for serious heavy calculations to be possible. In particular, free energy perturbation calculations offered, in principle, the opportunity to compute genuine free energy differences incorporating solvent molecules and very realistic simulations by either molecular dynamics or Monte Carlo techniques (Figure 3). Like others, we used this to calculate

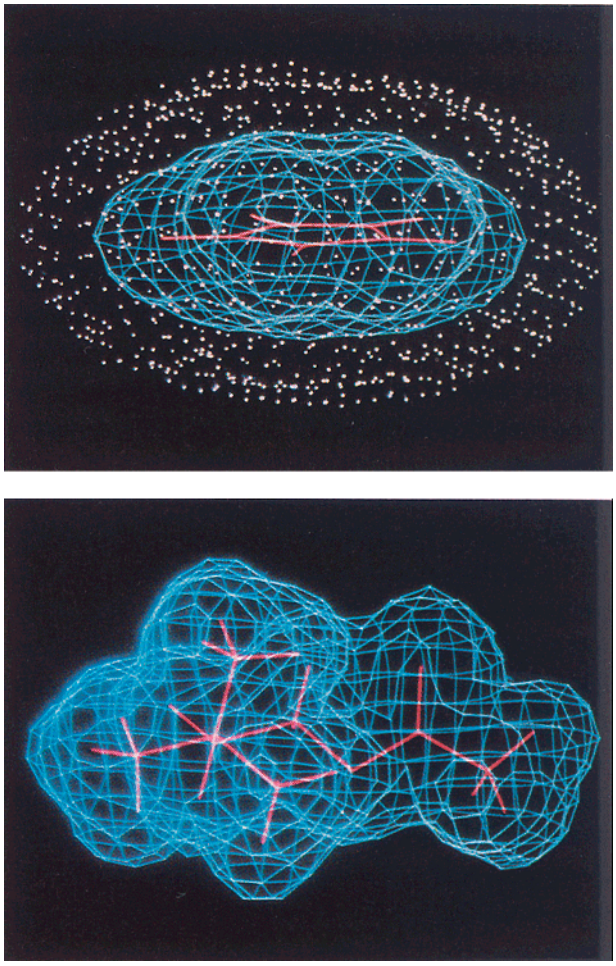

Figure 2. The first colored molecular graphics pictures. Reprinted from *Endeavour*, Vol. 7, W. G. Richards and L. Mangold, Computer-Aided Molecular Design, pp 2−4, Copyright 1983, with permission from Elsevier.[12b]

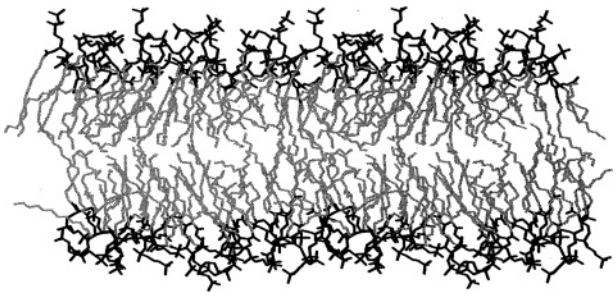

Figure 3. Simulation of a biological membrane. Reprinted with permission from *Biophysical Journal*.[32] Copyright 1994 Biophysical Society.

differences between binding energies of ligands to a receptor binding site but more uniquely showed that we could calculate redox potential differences[17] and partition coefficients,[18] crucial as they are respectively to bioreductive drugs and to membrane transport.

Quinones are one class of molecules that have been used as bioreductive agents. The difference in redox potentials of two quinones Q and Q′ (Table 3) can be obtained from the free energy for the equation

$$Q'H_{2(aq)} + Q_{(aq)} \rightarrow QH_{2(aq)} + Q'_{(aq)};$$
$$\Delta\Delta G = -nF(E_Q - E_{Q'})$$

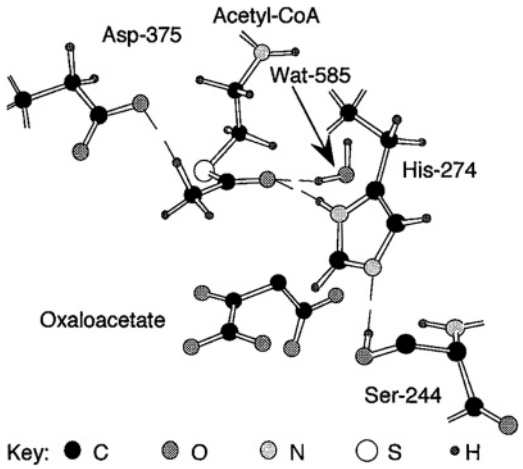

Figure 4. Detail of the active site of the citrate synthase−substrate complex after QM/MM minimization. This is a preprint from an article published in *Proteins: Structure, Function, and Genetics* **1997**, *27*, 9−25 (http://www.interscience.Wiley.com/).[21c] Reprinted with permission. Copyright 1997 John Wiley & Sons, Inc.

Table 3. Computed Redox Potentials by Free Energy Perturbation

redox potential difference between 1,2 benzoquinone and 1,4 benzoquinone	
theory	−0.072 V
experiment	−0.092 V

This in turn can be obtained from the following thermodynamic cycle:

$$\begin{array}{ccc} Q'H_{2(g)} + Q_{(g)} & \xrightarrow{\Delta\Delta G_{(g)}} & QH_{2(g)} + Q'_{(g)} \\ \Delta G_{(Q'H_2,hyd)} \downarrow & & \downarrow \Delta G_{(Q,hyd)} \quad \Delta G_{(Q'H_2,hyd)} \downarrow \quad \downarrow \Delta G_{(Q',hyd)} \\ Q'H_{2(aq)} + Q_{(aq)} & \xrightarrow{\Delta\Delta G_{(tot)}} & QH_{2(aq)} + Q'_{(aq)} \end{array}$$

$$\Delta\Delta G_{(tot)} = \Delta G_{(QH_2,hyd)} - \Delta G_{(Q,hyd)} + \Delta G_{(Q',hyd)} - \Delta G_{(Q'H_2,hyd)} + \Delta\Delta G_{(g)}$$

where $\Delta G_{(QH_2,hyd)} - \Delta G_{(Q,hyd)}$, the difference in free energies of hydration of QH_2 and Q, can be obtained using the free energy perturbation relationship (Figure 4).

By the 1990s, computational contributions were so well established that all pharmaceutical houses employed teams of specialists. The standard activities in which we played a part included determining protein structures by homology modeling where we focused attention on cytokines,[19] on DNA and in particular triple helix formation,[20] and on enzyme mechanisms using a combination of techniques for both gas and solution-phase computation of potential surfaces.[21]

Current Research

I have always spread myself, perhaps a little thinly, moving to new approaches whenever something cropped up that might have application in the drug discovery field. We were, for example, among the earliest groups to apply neural networks[22] and introduced a variety of novelties into structure−activity studies.[23]

In the past few years the wealth of adaptable software originally developed for pattern recognition has provided a fruitful source, as have ideas on novel ways of

Figure 5. Alignment between DFKi and the protein TOMI. Reprinted with permission from *Journal of Chemical Information and Computer Sciences*.[25b] Copyright 2000 American Chemical Society.

representing structures.[24] Daniel Robinson during his graduate student work adapted ideas from computer vision to give a novel method of molecular alignment that is both fast and accurate[25] (Figure 5). Above all, this key step in predicting the nature of a binding site from knowledge of those molecules that bind to it can now be applied to molecules of very different sizes.

From the area of medical imaging has come software to find the binding site of a particular ligand on a protein of known structure. I believe that this type of problem will become increasingly important as synchrotron facilities yield more and more protein structures, but the binding site still has to be defined. The software that takes a multiscale approach[26] treats the ligand first as a point and finds those volumes of three-dimensional space where the binding site could not be. The small molecule is then treated as a two-point representation and the space of possible binding is further reduced and then by a three-point representation and so on. Using only a personal computer, we can find binding sites in a couple of minutes.

This software was used by us[27] to define the binding site of a key tetrapeptide on the protection antigen that forms part of the anthrax toxin and enables one to define a target for a drug to combat anthrax (Figure 6).

More recently members of my group have used the software that can now deal with a flexible ligand to investigate the so-called glutamate receptors in plants.[28] This study gives very strong indications that of the 20 gene sequences supposedly coding for glutamate receptors, 19 are in fact almost certainly glycine receptors, implying that ion channels in plants as in mammals are gated by glutamate and glycine, necessitating some revision of ideas of the evolutionary time scale (Figures 7 and 8).

Distributions

Reduced to its most basic, drugs are small molecules that bind to specific binding sites on proteins. Once the binding site is known to atomic resolution, the key aspect of drug discovery is finding the best ligand for the site, after which secondary properties such as

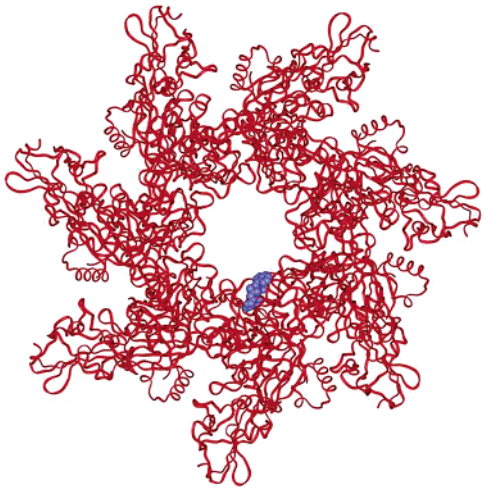

Figure 6. Target site for an anti-anthrax drug.

adsorption, distribution, metabolism, and excretion become important. Since there are an increasing number of possible targets as a result of structural genomic initiatives and a variety of crude methods of calculating the binding energy of a druglike molecule to a protein, the obvious step is to try molecules one at a time from a huge database of druglike structures.

This is the perfect problem for distributed computing: a so-called embarrassingly parallel problem.

Once again adapting ideas generated in an unrelated field, we have taken up the ideas from the SETI project, the search for extraterrestrial intelligence whereby radio signals from space are farmed out to personal computers worldwide with software using unused cycles embedded in a screensaver to test whether any of the billions of recorded signals is an intelligent message. It is a nice computing idea, but no positive result has emerged. Following the same line,[29] in collaboration with United Devices of Austin, TX, Keith Davies[30] of Find-a-Drug, and later Accelrys Inc., we have set up a distributed network of quite astounding power. Since the project was launched in April 2001 we have amassed over 2.5 million personal computers in some 200 countries, yielding over 300 000 years of CPU time. Even by the most conservative estimate we have a 150 teraflop machine capable of screening in silico billions of druglike molecules in a week or so. Note that the world's biggest supercomputer only weighs in at about 40 teraflops. The chief extension to SETI is the large number of positive hits that have to be sent back to a central server and then analyzed.

To feed the facility, we have a database of 35 million druglike molecules assembled by Keith Davies and latterly Dan Butler. These structures come from suppliers' catalogues and from combinatorial libraries with the computer generating extra reagents and hence products. However, all these molecules are available for purchase or we have a published synthetic route. Furthermore all the molecules are druglike in that they have been filtered to satisfy Lipinski's criteria[31] and unstable or reactive substructures have been eliminated. For very rapid binding estimates using pharmacophore pattern matching, each of the 35 million starting structures can have 100 de novo derivatives created by changing groups with alternatives generated

```
                  1                   10                  20                  30
RatGlurB          - - T E I A Y G T L D S G S T K E F F R R S K I A V F D K M W T Y M R S A E P
RatKain1          - - T K I E Y G A V R D G S T M T F F K K S K I S T Y E K M W A F M S S R Q Q
NR2a              Y S P P F R F G T V P N G S T E R N I R N N - - - - Y P Y M H Q Y M T K F N Q
NR2b              F S P P F R F G T V P N G S T E R N I R N N - - - - Y A E M H A Y M G K F N Q
NR2c              Q Y P P F R F G T V P N G S T E R N I R S N - - - - Y R D M H T H M V K F N Q
NR2d              Q Y P P L K F G T V P N G S T E K N I R S N - - - - Y P D M H S Y M V R Y N Q
AtGLR1.1          - - - - - - H Q M V F G G S T T S M T A K L - - - - - - - - - - - - G S I N A
AtGLR1.2          - - - N E D Y V G H L S G S L I A N A A L T - N S S L R A M R - - L L G L N T
AtGLR1.3          - - - N E D Y V G H L S G S L I A N V A L T - S S S L R A M R - - S L G L N S
AtGLR1.4          - - - S N E N I G F F S A S I A A N V V N D - N P T F Q G P R - - Y K G L K T
AtGLR2.1          L L A K G E S V G Y Q - S S F I L G R L R - D S G F S E A S - - - L V S Y G S
AtGLR2.2          L L H R G E T V G Y Q R T S F I L G K L N - E T G F P Q S S - - - L V P F D T
AtGLR2.3          L L E K G E T V G Y Q R T S F I L G K L K - E R G F P Q S S - - - L V P F D T
AtGLR2.4          V L A K G G P V A Y Q R D S F V L G K L R - E S G F P E S R - - - L V P F T S
AtGLR2.5          L R K S G V N I G Y Q T G S F T F E R L K - Q M R F D E S R - - - L K T Y N S
AtGLR2.6          L R N S G V N I G Y Q T G S F T F E R L K - Q M G Y K E S R - - - L K T Y D T
AtGLR2.7          L I K F N K N I G Y Q R G T F V R E L L K - S Q G F D E S Q - - - L K P F G S
AtGLR2.8          L I K N G D Y V G Y Q H G A F V K D F L I - K E G F N V S K - - - L K P F G S
AtGLR2.9          L I K N R D C V G Y Q G G A F V K D I L L - G L G F H E D Q - - - L K P F D S
AtGLR3.1          L I S S T G R I G F Q V G S F A E N Y M T D E L N I A S S R - - - L V P L A S
AtGLR3.2          S Y S A T A K L T N Q R S - - R H T H Q Q Q W T S W V S G R - - - L V P L G S
AtGLR3.3          L R E R D D P I G Y Q V G S F A E S Y L R N E L N I S E S R - - - L V P L G T
AtGLR3.4          L V T S N E P I G V Q D G T F A R N Y L I N E L N I L P S R - - - I V P L K D
AtGLR3.5          L I A S N E P I G V Q D G T F A W K F L V N E L N I A P S R - - - I I P L K D
AtGLR3.6          L Q T N H D P I G Y P Q G S F V R D Y L I H E L N I H V S R - - - L V P L R S
AtGLR3.7          L R A S E V P I G Y Q A G T F T L E Y L T Y S L G M A R S R - - - L V P L D S
NR1a              P S D K F I Y A T V K Q S S V D I Y F R R Q V E L S - - - - - T M Y R H M E K
NR3a              P S Q G F R F G T V R E S S A E D Y V R Q S - - - - F P E M H E Y M R R Y N V
NR3b              P S Q G F R F G T V W E S S A E A Y I K A S - - - - F P E M H A H M R R H S A
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Figure 7. Sequence alignment of purportedly glutamate receptors.

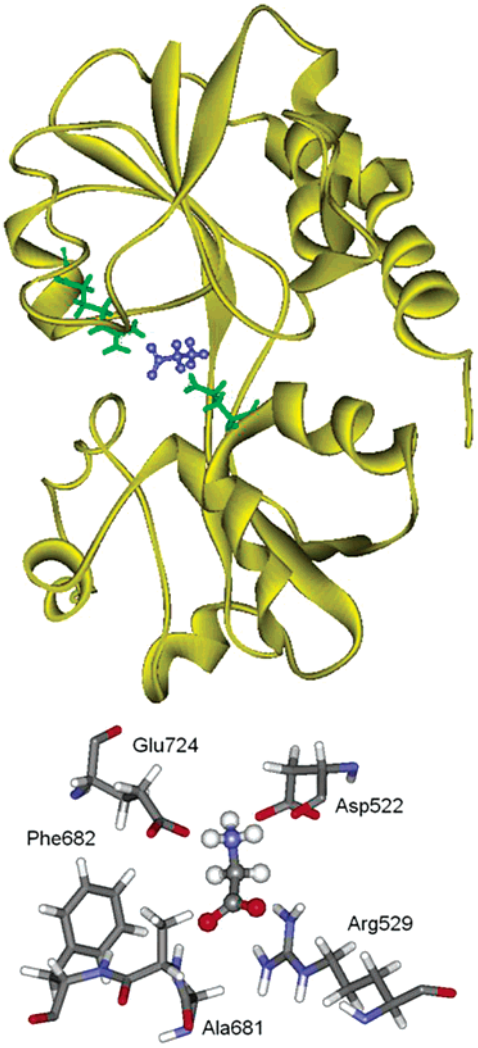

Figure 8. Glycine bound to the plant GLR 2.9 receptor. Reprinted with permission from *The Plant Journal*.[28]. Copyright 2003 Blackwell Publishing.

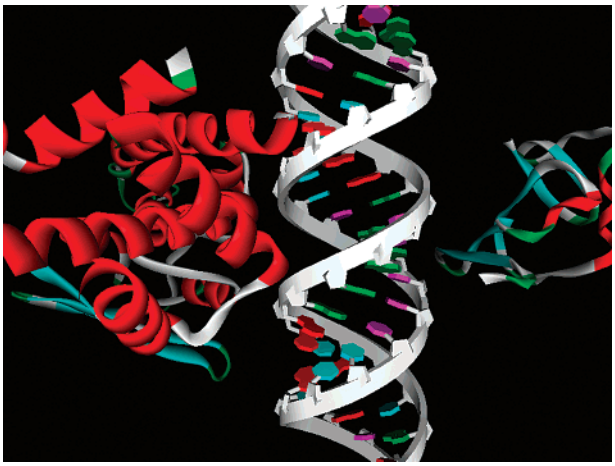

Figure 9. Smallpox target: topoisomerase.

using random selections. This gives a power greater than that available to any major pharmaceutical company and one that we are endeavoring to make available to the wider academic community and to researchers seeking drug leads against targets that industry cannot investigate, such as third-world diseases.

To date, we have looked at some 14 cancer-related targets and anthrax and smallpox, where the actual target was the topoisomerase used by variola to unpack its DNA, which it takes into the cell (Figure 9). Overall, we produce far more hits than could sensibly be synthesized and screened, but if we switch to more sophisticated binding energy calculations, these can be reduced to manageable proportions. In the case of the smallpox project, for example, Scott Kahn of Accelrys Inc. reduced the hits to some 900 "good" hits and about 50 "very promising" molecules. Fuller details of the screensaver project and the output can be found at www.chem.ox.ac.uk/curecancer.html.

Currently we are particularly interested in the results for potential phosphatase inhibitors because we see much of biology as a balance between kinases and

Table 4. Co-Workers of W. Graham Richards

Students, Postdocs, and Visitors			
John Horsley	Paul King	Joanne Taylor	ROMANO KROEMER
Tim Walker	CATHERINE BURT	Christine Walmsley	ANA CASTRO
Anthony Hall	GARRETT MORRIS	SUNG-SAU SO	PETER WINN
Reg Hinkley	JONATHAN ESSEX	SANJAY SANGHANI	AARON DINER
Alistir Todd	GRAHAM WORTH	STEVE GARLAND	XABIER LOPEZ
Jim Port	Richard Gilbert	Ankash Nandra	MEIR GLICK
John Raftery	Paul Boscott	Nia Neville	Juan Adelentado
Peter Scott	ADRIAN ELCOCK	ANABEL TODD	MASSOUD MAHMOUDIAN
Les Farnell	ANDY GOOD	CHARLOTTE DEAN	VIJAY COMBAR
Les Clyne	ADRIAN MULHOLLAND		AKIRA NAKAYAMA
Bob Hammersley	PAUL BAMBOROUGH		Myrna Gil
ELIZABETH COLBOURN	DAVID LOWIS	Jane Hammond	VERNON CHENEY
Ian Wilson	ALAN ROBINSON	Jennifer Wallis	FEDERICO GAGO
Stephen Moore	James Bradley	Gaynor Leggate	CRISTINA MENZIANI
TONY MARCHINGTON	Tom Barlow	Susan West	GYORGY FERENCZY
Chet Chung	STEPHEN DOUGHTY		Amatz Meyer
DAVID COOPER	Ivy Boey		MARIA RAMOS
VALERIE SACKWILD	Martin Parretti	SUK PING SO	Carl Schwalbe
Alda de Sousa	DANIEL ROBINSON	JILL GREADY	Alon Seri-Levy
Robert Elliott	PETER VARNAI	Harit Trivedi	Sakaya Shinomoto
Sandra Robins	Owen Walsh	Roger Humphries	Justin Caravalla
NEIL STUTCHBURY	STEWART ADCOCK	George Jaroskiewcz	ANDERSON COSER GAUDIO
CHRIS NAYLOR	BEN WEBB	Alistair Cuthbertson	TONY HOPFINGER
Ruth Holmes	MAYA TOPF	CHRIS REYNOLDS	DAVE WINKLER
Saira Mian	Ben Allen	IAN HAWORTH	MILAN REMKO
Pippa Bowen-Jenkins		GUY GRANT	
DAVE RICKETTS		Barry Hardy	
EDWARD HODGKIN	Brian Hill	JEFF ROTHMAN	
ANDREW SMELLIE	Mary Anne Cordeiro	PAUL LYNE	

phosphatases, and the industry has focused on the former during the past decade. In the next 10 years phosphatase inhibitors, of which we have some 120 000 examples after the first rough cut, seem more than likely to become serious commercial possibilities.

Commercial Activity

For many years I gave away software written in my group or passed it on for a notional fee with the stipulation that we were an academic group with no possibility of providing support or even detailed documentation. In 1989, partly for personal reasons, together with my former student Tony Marchington, we founded Oxford Molecular Ltd. The company was started with £350 000 of venture capital and had an initial public offering in 1994, after which it engaged in a string of takeovers in the U.S., acquiring CAChe, MacVector, and GCG Wisconsin, among other companies, and founded Cambridge Discovery Chemistry. At its height the company was valued at £450 million and at its lowest £30 million. At one time it had the largest share of the world bioinformatics market, about 25%, and the biggest share of the Japanese molecular modeling market. Of sales, 60% were in the U.S., and at its peak there were 400 employees with half of them being in the U.S. The company was finally sold in two parts: the synthetic part to Millennium Pharmaceuticals and the software business to Pharmacopeia, becoming part of Accelrys Inc. It thus gives me particular pleasure that this Award is sponsored by Accelrys, with whom we have excellent collaborations, using their Ligandfit software in the screensaver project.

My other quasi-commercial activity has been to raise $100 million to build a new Chemistry Research Laboratory, which was opened by HM The Queen in February this year. A novel aspect of that funding was obtaining $30 million from a City of London bank as an upfront sum in return for half of the University share of equity in spin-out companies from the Department of Chemistry. To date, our spin-out activities have contributed over $60 million to the central University, and since setting up the deal with the bank another six spin-out companies have been created.

Acknowledgment. I thank the American Chemical Society for the honor of being given this Award, and I thank its sponsors Accelrys Inc. Among the major funders of my research over the past 40 years, I must single out the National Foundation for Cancer Research and The Wellcome Trust. Collaborating with many of the world's major pharmaceutical companies has too been a rewarding experience because over the years the gap between academia and industry has narrowed and virtually disappeared. My chief thanks, however, must go to the body of students, postdoctoral workers, and visitors who have done most of the work. Table 4 gives a list with those still active in drug discovery research (in capital letters). Although some might think that the new laboratory in Oxford is likely to be my lasting legacy, that is not so. It is the students with whom one has had the pleasure to work with who are the real lasting inheritance.

Biography

W. Graham Richards obtained his Bachelors degree and Doctorate from the University of Oxford where he is currently Chairman of the Department, which is the largest in the Western world. Apart from a postdoctoral period in Paris and sabbaticals at Stanford and Berkeley, his whole scientific career has been at Oxford. His research has been largely on the use of computational chemistry in drug discovery, encompassing small molecules, proteins, DNA, and membranes. He has authored over 330 papers and 15 books, and among other awards he has received the Lloyd of Kilgerran Prize from the

Foundation for Science and Technology in 1996, the Mullard Award of The Royal Society in 1998, and the Italgas Prize in 2001.

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JM040136Y