of limited pipelines, increasing R&D costs, and the competitive pressure on marketed drugs and those with expiring patents. Many pharmaceutical companies have initiated rounds of mergers and acquisitions to cut costs. Steve Arlington of PriceWaterhouseCoopers (London, UK) predicted the operating environments and the search for new medicines in the next five years. He said that shareholder's returns in the top 20 pharmaceutical companies have averaged 22% during the past five years. There is an impending fall in these returns because R&D costs are continuing to rise at 10.8% per annum, whereas revenue from new drugs is only growing at a rate of 7%. If these companies launch 26 NCEs at an average cost of $500 million per drug during the next five years, the total shareholders' return will approach zero. He presented a new model with decreased dependency on 'blockbusters' and requiring transformation in all aspects of innovation and commercialization. This transformation needs to be accomplished in less time than it takes to develop a new drug.

Conclusion

Numerous new technologies are available for drug discovery and development processes. Collaboration of pharmaceutical companies with biotechnology companies providing genomics technologies and bioinformatics will play an important role in this process. Research and development of new biopharmaceuticals will require consideration of the economic aspects as well.

REFERENCES

1 Lindpaintner, K. (1999) Genetics in drug discovery and development: challenge and promise of individualizing treatment in common complex diseases. *Br. Med. Bull.* 55, 471–491

2 Martin, E.R. *et al.* (2000) Analysis of association at single nucleotide polymorphisms in APOE region. *Genomics* 63, 7–12

3 Quadroni, M. and James, P. (1999) Proteomics and automation. *Electrophoresis* 20, 664–677

4 Jain, K.K. Applications of biochip and microarrays systems in pharmacogenomics. *Pharmacogenomics* (in press)

Kewal K. Jain
Bläsiring 7
CH-4057 Basel,
Switzerland
tel/fax: +41 61 692 4461
e-mail: jain@pharmabiotech.ch
URL: http://pharmabiotech.ch

New PDE5 inhibitors: more selective than Viagra?

The fortunes of any pharmaceutical company that can produce a better drug than sildenafil – more commonly known by its tradename of Viagra – are bound to rise. Researchers at Bristol-Myers Squibb Pharmaceutical Research Institute (Princeton, NJ, USA) recently reported that they have identified compounds that, *in vitro* at least, appear to have a more selective action than sildenafil[1].

Mechanism of action of sildenafil

Sildenafil (Fig. 1), which was developed by Pfizer (Sandwich, UK) works by inhibiting the phosphodiesterase type 5 (PDE5) enzyme. In the healthy man who does not have difficulty achieving an erection, sexual stimulation leads to the release of nitric oxide within the blood vessels of the penis. A cascade of biochemical events follow, leading to the production of cGMP, and causing vasodilatation and increased blood flow into the corpus cavernosum of the penis which becomes erect. Simultaneously, PDE5 continues to break down the cGMP. However, in erectile dysfunction, cGMP is produced in inadequate quantities and what is produced is metabolized by PDE5.

Sildenafil inhibits this breakdown, allowing cGMP levels to build up so that an erection occurs. Occasional side effects include nausea, headaches, flushing and visual disturbances such as sensitivity to light and a blue tinge to what is seen. David Rotella, first author on the paper and Senior Research Investigator at Bristol-Myers Squibb, hypothesizes that some of these side effects might be caused by the nonselective inhibition of other PDEs, such as PDE1 and PDE6.

New inhibitors of PDE5

Initially, Rotella and coworkers embarked on this project to identify compounds to treat erectile dysfunction because at that time, no such products were on the market. Rotella said, 'We saw this as an excellent drug discovery opportunity in a market that we thought was capable of giving us the opportunity to improve people's quality of life.'

 1359-6446/00/$ – see front matter PII: S1359-6446(00)01535-X

Like researchers at Pfizer, the Bristol-Myers Squibb team began their search with a known inhibitor of PDE5 called zaprinast (Fig. 1), which they modified to produce new compounds using rational drug design. Ultimately, they identified a position in the core structure that produced compounds that were, *in vitro*, more selective than sildenafil against other PDE enzymes. Having identified that site, they then focused on optimizing the substituents at that site to produce a compound that was both more potent and more selective than sildenafil.

The most promising compound, currently known as '14' (Fig. 1), is an *N*-3-(fluorobenzyl)-imidazoquinazolinone. Its chemical name is 1-[3-[1-[(4-fluorophenyl)methyl]-7,8-dihydro-8-oxo-1*H*-imidazo[4,5-*g*]quinazolin-6-yl]-4-propoxyphenyl]carboxamide. Tests conducted by Rotella and his colleagues showed that the IC_{50} of '14' against PDE5 was 0.48 ± 0.1 nM, while that of sildenafil was 1.6 ± 0.5 nM.

The team also evaluated '14' with an animal tissue model of erectile dysfunction, which uses strips of tissue from the corpus cavernosum of the rabbit penis. Normally, when the corpus cavernosum of the rabbit (or human) relaxes, blood flow into the penis increases and outflow decreases, leading to an erection. In this model, Rotella and his colleagues found that '14' was as potent as sildenafil in achieving relaxation of pre-contracted rabbit penile smooth muscle at concentrations of 30 nM and 300 nM of both '14' and sildenafil.

Only tests on '14' in humans will show if this new compound has fewer side effects than sildenafil. John Macor, coauthor of the paper and Associate Director of Discovery Chemistry at Bristol-Myers Squibb added, 'It is known that PDE6 is present in the eye, and some of the visual side effects that have been associated with the use of sildenafil are believed to be the result of this drug's modest selectivity against PDE6. These compounds have improved selectivity versus PDE6 so you could infer that they might have fewer side effects – but until we prove that PDE6 is the cause of sildenafil's side effects, we have no way of knowing.'

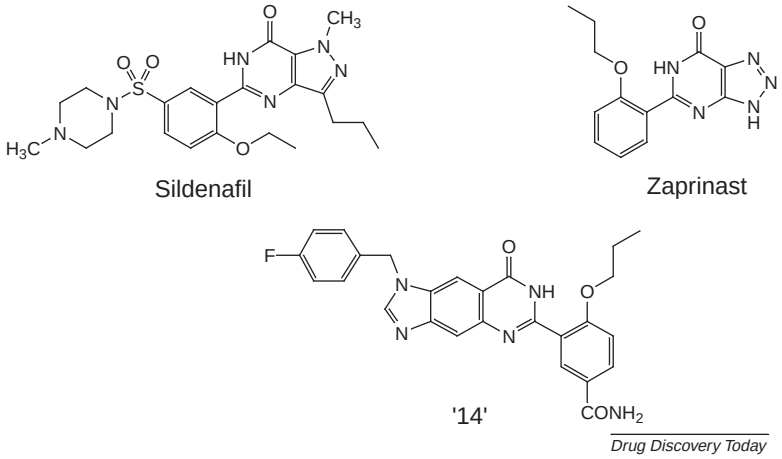

Figure 1. *The chemical structures of sildenafil, zaprinast and '14'.*

REFERENCE

1 Rotella, D. *et al.* (2000) *N*-3-substituted imidazoquinazolinones: potent and selective PDE5 inhibitors as potential agents for treatment of erectile dysfunction. *J. Med. Chem.* 43, 1257–1263

Sharon Kingman

Technology collaboration...

Axon Instruments (Foster City, CA, USA) has entered into a collaboration with **AstraZeneca** (London, UK) to develop an automated electrophysiology system for higher-throughput drug screening, which would represent a major step forward in research into ion channel and G protein-coupled receptor (GPCR) targets. Under the terms of the agreement, AstraZeneca will supply a prototype instrument and key technology to Axon, who will then develop it into a production-quality drug screening system for non-exclusive use by AstraZeneca and for sale by Axon to other companies.

'Ion channels are important therapeutic drug targets, but traditional assays are indirect and suffer from many shortcomings such as false-positives, false-negatives, lack of specificity, inadequate quantitation and absence of control of the voltage across the ion channels,' said Alan Finkel, Founder and CEO of Axon Instruments. He added, 'The solution to these shortcomings is to directly measure the tiny currents passed by the ion channels.'

Edwin Johnson, Section Head of Molecular Pharmacology at AstraZeneca said, 'We are pleased to work with Axon Instruments in the development of a system that will make it possible for us to improve the efficiency of our ion channel drug discovery program. The Axon system will also allow us to cost-effectively implement these screening programs.'