in terms of the vertical corporate strata as well as the horizontal. This enables rational selection of projects to progress. Importantly, it also means that funding and budget decisions can be made on the basis of dialogue between different levels of management. So often, the relationship is one of parent–child. The consequence is a 'liar's game' decision spiral: project proposers know that management will cut any project budget as proposed, so inflate their figures accordingly; management expect proposers to submit inflated figures, so cutting the budget becomes a reflex. The Mathesons argue that this is best resolved by looking at projects in terms of the predicted value consequences of three 'what if' project alternatives versus the current plan:

- Buy-down plan. 'What if the project's costs had to be reduced?
- Buy-up plan. What if more money were available?
- Salvage plan. Abandon the plan, conserving as much value earned as possible.

Movie microcosm

Common themes can be found in many industries, says Jim Matheson, 'take the movie industry – on the face of it, it is very different. If you look closely, the parallels with pharmaceutical portfolio management are striking, thousands of candidate scripts are screened, cycle times have been radically reduced, there are a few major players with a large number of satellites, each major player has an annual target for product launches, and will expect, say, one blockbuster in twenty, and it is imperative to squeeze the maximum value from each project.'

Core principles and benchmarking

David Matheson has defined nine principles that form the cornerstone of the SDG philosophy (Box 1). These principles form the basis for a 'IQ test' benchmarking exercise. The test can be re-evaluated over time to provide a measure of change, hopefully improvement, in performance.

According to Leigh Thompson, formerly Chief Scientific Officer at Eli Lilly 'the fundamental principles they outline were the basis for re-engineering of drug discovery and development at Eli Lilly and Company'. *The Smart Organization; Creating Value through Strategic R&D* is available in hardback for $29.95 from Harvard Business School Press (Web: http://www.hbsp.harvard.edu).

David Hughes

BAF and neonatal brain damage

Inhibitors of the caspase group of enzymes can protect newborn rats from further brain damage following an interruption to the blood supply, according to research published recently by a US team. The discovery could act as a model for establishing the viability of the compounds as potential drugs for minimizing the often devastating effects on the infant brain during or before birth.

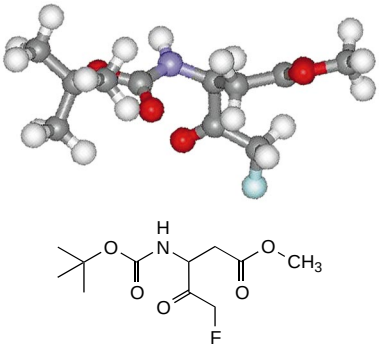
The hydrolyzing cysteine caspase protease enzymes have been associated with programmed cell death (apoptosis); they are used by the body to control cell turnover, but are also involved in unwanted tissue degradation in some diseases. Numerous biotechnology companies have identified the potential of blocking these enzymes. For instance, following a stroke or other blockage to brain tissue, the damage induced by anoxia is often associated with the apoptotic effects of these enzymes.

Effective caspase inhibitor

David Holtzman and former postdoctoral worker Yu Cheng and their colleagues at the Washington University School of Medicine in St Louis, MO, USA have shown that one caspase inhibitor, known as BAF – boc-aspartyl(*O*-methyl)-fluoromethylketone (see Figure) – protects newborn rats from damage [Cheng, Y. *et al.* (1998) *J. Clin. Invest.* 101, 1992–1998]. 'To our knowledge, this is the first demonstration that delayed treatment with a caspase inhibitor, even when given systemically, can be neuroprotective in a brain-injury model', says Holtzman. He adds that if the inhibitors prove to be non-toxic and pass through clinical trials successfully, then they could provide a useful window of at least several hours when one could administer them.

An interruption to the blood supply to the brain *in utero* or during or after birth is the largest contributor to brain degeneration in children. The range of consequences includes mental retardation, seizures, cerebral palsy and learning difficulties.

Holtzman's rat model mimics the condition by interrupting the blood supply to one side of a newborn rat's brain and briefly lowering the oxygen partial pressure of its air supply. This procedure kills neurones, resulting in loss of brain tissue. Holtzman and his colleagues have found



BAF [boc-aspartyl(O-methyl)-fluoromethylketone] is a caspase inhibitor that has been shown to inhibit apoptosis. It may have potential as a neuroprotective agent for neonatal brain damage.

1359-6446/98/$19.00. PII: S1359-6446(98)01216-1

that by contrast to the rapid lysing of neurones that takes place in adults with head injury or stroke, many of the neurones took from 6 to 24 hours to shrink and die in this model. The team found that caspase enzymes were activated just before this slow death as if the cells were undergoing normal apoptotic death. This hinted to Holtzman that a caspase inhibitor may be successful in saving anoxic brain tissue in neonates even if administered several hours after the potentially damaging event. A major question in the field is whether it would be clinically useful to use caspase inhibitors to prevent apoptosis.

Control of tissue loss

He and his team decided to test the idea using BAF, a modified amino acid previously shown to inhibit common apoptosis. The researchers injected BAF into the brains of some rats immediately before the oxygen supply was reduced and into others 3 h later. After one week, the researchers examined brain slices. They found that in the rats that received no BAF treatment there was extensive tissue damage in the affected hemisphere. The cortex, hippocampus and striatum had shrunk, and the fluid-filled ventricles had expanded. But a very different picture emerged when they analysed the BAF-treated rats. 'On average, the control animals lost about 50% of the tissue in these regions, whereas the BAF-treated animals lost only about 20%,' Holtzman explains. 'The difference between the BAF-treated animals and the control animals was so great that it's hard to imagine that treatment with BAF or similar compounds wouldn't be worth exploring as potential treatments in humans. That issue obviously needs to be investigated further, however,' he adds.

David Bradley
http://www.camsoft.com/elemental/

Book reviews

'Emerging Drugs: the Prospects for Improved Medicines'

edited by W.C. Bowman, J.D. Fitzgerald and J.B. Taylor, Ashley Publications, 1998. £395, $690 (vi + 397 pages) ISSN 1361-9195

This is the third annual volume in this successful series from pharmaceutical research specialists Ashley Publications (http://www.ashley-pub.com). This edition has further refined the approach to providing succinct topical information in key therapeutic areas in the context of the industrial setting. Each chapter (there are 24) is structured in eight sections to convey a comprehensive picture. The sections within each chapter are:

- Concise background to the subject matter
- Assessment of medical need for alternative or novel therapies
- Assessment of the market and anticipated changes over time
- Summary of current research goals
- Outline of the scientific rationale for the approach(es) considered
- Analysis of the competitive environment
- Discussion of potential development issues
- Overall editorial analysis

The editors have done an excellent job in selecting a team of authors, primarily from the industrial sector. Subjects covered are too numerous to mention here, but representative topics include insulin-sensitizing agents, benign prostatic hyperplasia, tyrosine kinase inhibitors as anticancer agents, inhibition of apoptosis, phospholipase A_2 inhibitors, antisense oligonucleotides and therapeutic vaccines. This volume, like its predecessors, is likely to find its way onto the shelves of many company libraries.

'Global Drug Discovery: Exploiting Technologies to Accelerate Drug Development'

L.M. Savage (Managing Editor), IBC Library Series, 1998. $1500, commercial; $895, academic (over 600 pages) ISBN 1-57936-086-6

One of the most professional organizers of conferences specializing in topics relevant to drug discovery, IBC, is now making the proceedings of selected events available on a commercial basis. *Global Drug Discovery* is based on presentations from three major IBC conferences held in 1997 (two US, one UK). The two volume book covers the whole spectrum of activities in drug discovery. By definition, the content is not comprehensive, but authors' original manuscripts or, alternatively, transcripts of the talk are included in a range of discovery areas: new technologies for lead discovery and optimization; generating, identifying, and validating new targets; bioinformatics; laboratory automation, miniaturization technologies, and robotics; strategic management of drug discovery and poster presentations. There are twenty two chapters in all and most contributors are from the pharmaceutical and biotechnology industries.

The price and focus of this work mean that it will be relatively unattractive to academic centres. However, companies may feel that this represents a worthwhile investment, as it is a permanent record and avoids the cost and inconvenience of sending a staff member to the meeting. What can never be captured on paper, however, is the networking value of 'being there'. Nevertheless, for those whose T&E budget is a little stretched this year, this may represent a significant short-cut.

David Hughes