could increase or decrease each year. This expanded analysis yields the same states at product launch, but it is now also possible to plan the decision situations during R&D. The expanded decision tree is equivalent to the binomial trees that are used to simulate market fluctuations in financial theory [2].

The solution of the decision tree is just a slightly more-complex scenario analysis. At each node, the potential (probability adjusted) revenue is compared with the capital already invested. If the capital invested is greater than the potential revenue, then the project is abandoned. With this type of decision tree analysis, all the options to abandon the project during the development of a compound can be considered. Real options valuation is nothing more than solving this decision tree [3].

Advantages versus disadvantages

Frequently raised arguments against the use of real options are that real options are difficult to understand, that this approach relies heavily on hypothesis and that sales revenues are not volatile enough to justify a real options valuation. Although real options are not trivial, we have shown that real option valuation is not much more than reiterated scenario analysis. The argument that the real options approach is reliant on hypothesis is aimed primarily at the modeling of market uncertainty. Scenario analysis and Monte Carlo simulations deal with the same problems. DCF assumes the cash flows to be of a predetermined size, which is a hypothesis as strong as assuming a particular probability distribution. Considering the issue of sales revenues, examination of the sales returns of medical compounds on the market illustrates the stability of sales revenues; the healthcare market is rather predictable. However, it must be kept in mind that until the product is on the market the efficacy of the product and client acceptance are unknown parameters. The clinical development phase helps to remove this uncertainty. During R&D, the uncertainty concerning the potential sales revenues is much higher because the levels of efficacy and safety of the product are only partially known. Real options valuation is the only method that assumes that the management will react to changes in the factors that influence the revenue (value drivers) of a project.

Biotechnology puts the techniques that are necessary to address specific diseases and syndromes into the hands of researchers. Typically, the targeted patient group is smaller than the patient group of symptom-fighting pharmaceutical compounds. The requirement for managerial flexibility is particularly high for focused medications that have a relatively small target group. The expected sales revenues are not significantly larger than developmental costs and a negative turn in the market could easily result in sales revenues falling below developmental costs. The case study by Borissiouk and Peli (O. Borissiouk and J. Peli, MSc thesis, University of Lausanne, 2002) came to the same conclusion – for projects with moderate potential, real option valuation is the most suitable approach.

Conclusion

The hypotheses underlying real option valuation are not as unrealistic as some would like them to be. Moreover, the complexity of this approach is not an impassable obstacle. Real options provide a valuable insight into the scenarios that could arise during a project. This is particularly important for highly specific products that stem from biotechnological discoveries.

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Neurodegenerative disease research in the 21st Century

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The *Screentech World Summit* meeting, which was organized by IBC Life Sciences (http://www.ibc-lifesci.com) and sponsored by Southern Research Discovery (http://www.southernresearch.com), was held in San Diego, CA, USA on 21–25 April 2004. The conference comprised four concurrent sessions that covered neurodegenerative diseases, protein

kinases and phosphatases, protease inhibitors and HTS and assay technologies.

Identifying the targets

Rudolph Tanzi (Harvard Medical School; http://www.med.harvard.edu) opened the neurodegenerative disease session with a review of the current state of Alzheimer's disease (AD) genetics. Rare genetic mutations linked to AD, for example, those associated with familial forms of AD (FAD), have a low prevalence but a high penetrance (carriers of FAD mutations will invariably develop signs and/or symptoms of the disease). By contrast, other genetic mutations linked to the development of AD, such as the well-characterized ε4 allele of apolipoprotein E, have a high prevalence (~25% of the population carries at least one ε4 allele), but a low penetrance; there is a 2–4 fold increase and an 8–10 fold increase in the probability of developing late onset-AD (LOAD) disease when an individual carries one ε4 allele or two ε4 alleles, respectively. Tanzi went on to present research on a genetic-based approach that centers on the identification of specific genetic variants with functional links to the 'amyloid β-peptide (Aβ) life-cycle'. Deposition of Aβ in brain parenchyma is widely believed to be causative to the cognitive decline that is associated with AD pathogenesis (the 'amyloid-cascade' hypothesis of AD pathogenesis). Comparison of low and high prevalent genetic mutations enables the identification of genetic markers that might be associated with the more common forms of LOAD, thus increasing the reliability with which AD can be predicted and enabling earlier therapeutic intervention. In addition, this approach can identify potentially novel druggable targets.

FAD genetic mutations result in the abnormal production and early accumulation of Aβ, which is a 4 kDa peptide formed from the proteolytic cleavage of the amyloid precursor protein (APP). Endogenous molecules that are associated with Aβ production (e.g. the β- and γ-secretases) and Aβ clearance (e.g. insulin-degrading enzyme, neprilysin and immunotherapeutic-based approaches) are the current focus of drug discovery efforts for AD therapy. Presentations by Martin Citron (Amgen; http://www.amgen.com) and Sukanto Sinha (Elan Pharmaceuticals; http://www.elan.com) indicated that the identification and cloning of β-secretase have invigorated pharmaceutical companies to focus drug discovery programs on inhibiting the production of Aβ. Analysis of Aβ levels in transgenic mice genetically engineered to lack expression of β-APP cleaving enzyme (BACE) confirms that this enzyme is the penultimate secretase responsible for Aβ generation in brain. Although BACE-deficient mice seem to be impaired in their performance of some behavioral tasks, the overall rarity of an overtly detrimental phenotype lends further support to efforts aimed at inhibiting β-secretase activity to effect decreases in levels of Aβ production and/or accumulation. After nearly a decade of what has primarily been the unsuccessful targeting of therapeutics at the γ-secretase cleavage site, which is now thought to be an enzymatic complex composed of at least four proteins and appears to be involved in the regulated cleavage of other proteins such as Notch, the identification of small molecules that can penetrate the brain and that are selective towards BACE is a priority. However, Jeffrey Nye of Johnson & Johnson Pharmaceutical Research & Development (http://www.jnj.com/home.htm) indicated that although modulation of γ-secretase activity is more complex, this approach might be the mechanism of action of some nonsteroidal anti-inflammatory drugs.

Harnessing endogenous capability

Recent evidence from preclinical transgenic mouse models suggests that modulating particular endogenous inflammatory processes could be beneficial in removing deposited Aβ. Joe Rogers (Sun Health Research Institute; http://www.sunhealth.org) has focused on dampening the destructive effects of the inflammatory response in the brain (e.g. increased cytokine levels in response to Aβ) while simultaneously maintaining the inherent ability of microglia to phagocytose Aβ. Pretreatment of primary cultures of microglia generated from rapid-autopsy material (from age-matched control and AD brain) with indomethacin and anti-Aβ antibody resulted in the efficient opsonization and subsequent degradation of Aβ without the concomitant upregulation of cytokines that are typically associated with the 'activated' state.

Could mobilizing endogenous neuronal stem-cell populations efficiently repair damaged tissue and potentially stimulate reformation of damaged synapses? Lee Rubin (Curis; http://www.curis.com) has carefully dissected the signaling pathway associated with sonic hedgehog (Shh) and has developed small-molecule agonists that mimic the actions of hedgehog (Hh), which is the endogenous ligand of Shh. The Hh pathway is activated following ischemia, and agonists administered after the insult can reduce the amount of tissue damage. In addition, research suggests that small-molecule agonists of Hh signaling initially reduce the level of neuronal cell death that is typically observed immediately after ischemic insult and then later stimulate neural replacement, thereby providing neuroprotective as well as regenerative benefits.

Efficient entry of a compound into brain is one of the first hurdles neuroscientists tackle as they progress clinical compounds for the therapy of various neurodegenerative diseases through the drug discovery chain.

Although specific compound properties (e.g. molecular weight <500 daltons and <8–10 H-bonds) assist with efficient brain delivery, they do not guarantee successful penetration of the compound into the brain. What about molecules, such as growth factors, that are obviously too large and bulky for traditional brain delivery? William Pardridge (University of California, Los Angeles; http://www.ucla.edu) suggests that efficient delivery of large growth factor-like molecules to brain can be achieved by exploiting specific receptors (e.g. the transthyretin receptor) that are located at the blood–brain-barrier. In theory, generating a 'Trojan' horse delivery system that comprises a transthyretin Fc-receptor fused with the protein and/or growth factor of choice should enable the efficient delivery of large molecules to the brain.

Characterizing and developing models

Lit Fui Lau (Pfizer; http://www.pfizer.com) described neurofibrillary tangles – the 'other' neuropathological hallmark of AD. Whereas AD research has benefited from robust models of Aβ and amyloid deposition, until recently, models that replicate neurofibrillary tangles have been scarce. Transgenic mice that overexpress specific components of the kinase-signaling pathway thought to be involved with neurofibrillary tangle formation have provided tools for investigators to begin examining this complex pathway. Karen Duff (New York University, Nathan Kline Institute; http://www.med.nyu.edu/Psych) has used transgenic mice overexpressing cdk-5 to characterize an increase in phosphorylated epitopes of tau as potential early (phospho-serine 202) versus later markers (phospho-serine 396 and phospho-serine 404) of neurodegeneration. Moreover, transgenic mice that are deficient in mouse tau but overexpress an artificial human tau chromosome appear to display dystrophic neurites (Alz 50 staining) and intraneuronal accumulation of tau (determined by thioflavin-S staining). Although the characterization of this model is presently incomplete, these initial results suggest that this particular gene construct might replicate more closely neurofibrillary tangle formation in mice, a neuropathological requisite for the definitive diagnosis for AD.

Donald Kirsch (Cambria Biosciences; http://www.cambriabio.com) highlighted that, in addition to generating and characterizing new and improved mouse models that mirror the phenotypes of neurodegenerative diseases, researchers are continuing to use model organisms such as yeast, *Caenorhabditis elegans* and *Drosophila melangaster* to decipher the molecular mechanisms associated with disease pathways and to validate central nervous system (CNS) targets.

Robert Hughes of Prolexys Pharmaceuticals (http://www.myriad-proteomics.com) illustrated the use of proteomics in identifying novel targets in Huntington's disease (HD) and presented findings on the protein-binding partners of huntingtin, which is a large protein of as yet unknown function. However, the mutated form of huntingtin contains a glutamine repeat expansion and this form of the protein is thought to play a key role in HD. Hughes described the use of a fully automated yeast two-hybrid-screening system combined with mass spectrometry validation of proteins to generate a protein–protein interaction road map. By 'geographically' locating interacting partners, crucial protein–protein interactions can be mapped and small molecules that interfere with key interactions identified. However, as Lawrence Zaccaro (Pfizer) indicated, one key factor in the progression of model development is the availability of research tools, which should be readily accessible to academics, as well as members of the pharmaceutical industry.

Therapeutic potential – thinking outside the box

The second day of the neurodegenerative disease session opened with a challenge from Kevin Felsenstein (Johnson & Johnson Pharmaceutical Research & Development) for researchers to confront past failures and critique why particular compounds might have failed. A case study of compounds designed to target the M_1-muscarinic receptor revealed that treatment with these molecules resulted in cognitive enhancement with the efficient lowering of Aβ. However, additional data indicated that these compounds were relatively non-selective in targeting M_1-receptors and had dose-limiting side effects, which precluded their further development. These results should not eliminate muscarinic receptor modulation as a potential therapeutically viable target for drug discovery efforts – on the contrary, more-selective compounds should be pursued. Felsenstein challenged the group 'to think outside the box' when developing clinical compounds that could target novel pathways.

Compounds targeting specific pathways are now in the early stages of clinical trials. For example, CEP1347, which targets the Jun-*N*-terminal kinase pathway, is entering a combined phase II–III randomized double-blind clinical trial for the treatment of Parkinson's disease. Jeffrey Vaught (Cephalon; http://www.cephalon.com) cited preclinical animal studies that suggest the targeting of this pathway (and more specifically mixed lineage kinase) will produce clinical efficacy in patients. Additionally, Menelas Pangalos (Wyeth; http://www.wyeth.com) described antagonists of $5HT_{1A}$ receptors, which are negatively coupled to adenylate cyclase and located on postsynaptic glutamate receptors, that could provide

symptomatic relief from the cognitive deficits associated with AD by relieving a hyperactive serotonergic system. In preclinical assays using rodents and non-human primates (marmosets), improvements following compound administration were observed in a variety of behavioral and non-behavioral tasks. Prototypic compounds are now advancing through Phase II clinical trial testing.

Because of the reduced morbidity and mortality of the majority of those in the developed world suffering from neurodegenerative diseases, which dramatically reduced life expectancy in the 20th century, a challenge for this new century is to provide novel and therapeutically efficacious treatments for the prevention and/or treatment of these diseases. Toward that end, a constant theme of the presentations was the need to keep the patient in mind, because the effects of neurodegenerative diseases are devastating for patient and caregiver alike.