become standards in the anticancer armamentarium.

References

1 Olivier M.R. *et al.* (2002) The IARC TP53 Database: new online mutation analysis and recommendations for users. *Hum. Mutat.* 6, 607–614
2 Lane D.P. and Huff T.R. (2003) Drug discovery and p53. *Drug Discov. Today* 8, 347–355
3 Khuri F.R. *et al.* (2000) A controlled trial of intratumoral ONYX-15, a selectively-replicating adenovirus, in combination with cisplatin and 5-fluoruracil in patients with recurrent head and neck cancer. *Nat. Med.* 6, 879–885
4 Bell S. *et al.* (2002) p53 contains large unstructured regions in its native state. *J. Mol. Biol.* 322, 917–927
5 Boschelli D.H. (1999) Small molecule inhibitors of receptor tyrosine kinases. *Drugs Future* 24, 515–537

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Proteasome inhibitors in the treatment of cancer

Few biochemical fields have spurred such intense interest as that of proteolytic enzymes. Initial interest in protein degradation has advanced to create a pool of knowledge that can be, and has been, exploited for therapeutic purposes: the use of recombinant tissue-plasminogen activator has revolutionized the treatment of myocardial infarcts [1]; retroviral protease inhibitors enable control over HIV infection in many patients [2]; and inhibition of angiotensin-converting enzyme is included in effective anti-hypertension treatments [3]. Numerous drugs are now being developed to interfere with proteases crucial in the coagulation, inflammation and tumor metastasis. This development was inevitable because proteasome functioning appears to be disturbed in several pathologies. Moreover, some successful drugs, such as HIV protease inhibitors, certain chemotherapeutics and statins are already effective proteasome inhibitors.

The proteasome-mediated degradation of proteins serves not only as a waste bin for aged or unwanted proteins but also as a powerful regulatory system that controls the precise timing of activation or inhibition of cellular metabolic pathways [4]. This variety of functions results from, among other factors, the fact that proteasomes can be assembled into various complexes composed of a plethora of different subunits. They can therefore target and regulate, with exquisite specificity, cellular processes as diverse as cell cycle, antigen presentation, apoptosis and transcription factor activation [4].

Owing to this versatility and the fear of unpredictable toxicity, researchers were reluctant to consider the potential use of proteasome inhibitors *in vivo*. The rapid entrance of proteasome inhibitors to clinical trials has, therefore, been an unexpected occurrence. A recent article by Julian Adams in *Drug Discovery Today* [5] provides a good summary of what has recently happened in this field.

Each class of proteasome inhibitor affects the degradation of different protein substrates. Surprisingly, some proteasome inhibitors appear to induce apoptosis in tumor cells and to protect quiescent or terminally differentiated cells. We might soon be able to precisely identify such proteasome inhibitors that will specifically affect the degradation of proteins involved in tumorigenicity and tumor progression without affecting vital cellular processes that might result in concomitant toxicity. Early observations in murine tumor models and the results of initial clinical studies are indeed encouraging and indicate feasibility, safety and efficacy of proteasome inhibitors [6–9].

Although we do not understand all of the molecular mechanisms of such anti-tumor specificity, we eagerly await the results of ongoing clinical trials, to indicate the value of proteasome inhibitors. On the one hand, they could prove to be another disappointment in the search for a cure for cancer, in which case they could still be a valuable source of more effective combinations of anti-tumor treatments (they might also reduce drug resistance, sensitize tumour cells to radiotherapy or exert anticachetic effects). On the other hand, however, proteasome inhibitors might just prove to be true magic bullets.

References

1 The GUSTO Angiographic Investigators (1993) The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function and surviva after acute myocardial infarction. *N. Eng. J. Med.* 329, 1615–1622
2 Lederman, M.M. and Valdez, H. (2000) Immune restoration with antiretroviral therapies: implications for clinical management. *J. Am. Med. Assoc.* 284, 223–228
3 Lip, G.Y. and Beevers, D.G. (2001) ACE inhibitors in vascular disease: some progress, more hope. *J. Hum. Hypertens.* 15, 833–835
4 Naujokat, C. and Hoffmann, S. (2002) Role and function of the 26S proteasome in proliferation and apoptosis. *Lab. Invest.* 82, 965–980
5 Adams, J. (2003) Potential for proteasome inhibition in the treatment of cancer. *Drug Discov. Today* 8, 307–315
6 Orlowski, R.Z. *et al.* (1998) Tumor growth inhibition induced in a murine model of human Burkitt's lymphoma by a proteasome inhibitor. *Cancer Res.* 58, 4342–4348
7 Teicher, B.A. *et al.* (1999) The proteasome inhibitor PS-341 in cancer therapy. *Clin. Cancer Res.* 5, 2638–2645
8 Aghajanian, C. *et al.* (2002) A Phase I trial of the novel proteasome inhibitor PS341 in advanced solid tumor malignancies. *Clin. Cancer Res.* 8, 2505–2511
9 Orlowski, R.Z. *et al.* (2002) Phase I trial of the proteasome inhibitor PS-341 in patients with refractory hematologic malignancies. *J. Clin. Oncol.* 20, 4420–4427

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