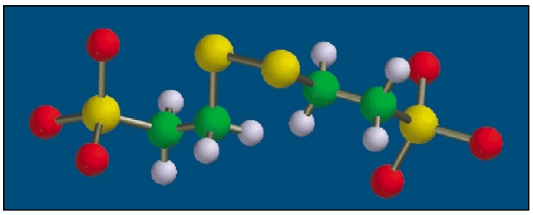
Supercomputer-designed drug protects against chemotherapy toxicity

BNP7787, a drug designed by Cray supercomputer technology to protect patients from the neurotoxic effects of chemotherapy, has just reached phase III clinical trials. "Preclinical work in rats has already demonstrated that BNP7787 can prevent toxicity induced by common chemotherapy treatments such as taxanes and cisplatin, while causing no side-effects," says Frederick H Hausheer (BioNumerik Pharmaceuticals, San Antonio, TX, USA).



Courtesy of BioNumerik

Computer-generated 3-dimensional structure of BNP7787

During the next few months, between 170 and 240 patients with metastatic breast cancer will be recruited. The trial will run for 24 weeks and will monitor aggregate neurotoxicity in two groups of women receiving weekly doses of Taxol (paclitaxel); one group will be given a pretreatment infusion of BNP7787 at a dose of 18.4 g/m^2; the other group will receive a control infusion. "We know from animal studies that the timing of the BNP7787 infusion is important, and so it will be given immediately after the hour-long Taxol treatment", explains Kathy Hurtado of BioNumerik. Results are expected in summer 2001. BNP7787 was given fast-track designation by the US Food and Drug Administration in July, 1999; if the results of phase III trials are good, the product could receive approval only 6 months after study completion.

BNP7787 is a water-soluble disulphide (disodium-2,2′-dithio-bis-ethane sulph-onate), which selectively inactivates the toxic monohydrated form of Taxol. "Approximately half of patients who are given weekly Taxol suffer nerve damage", points out Hausheer; currently, there is no way to prevent or treat this damage. BNP7787 has shown an excellent safety profile in phase I studies at doses of 41 g/m^2 in Europe and the USA. LD_{50} data show that BNP7787 has toxicity similar to substances such as aspirin and table salt. "In addition, BNP7787 does not appear to affect the ability of Taxol or other chemotherapeutic agents to cause tumour apoptosis", says Hausheer.

Epie Boven and Herbert Pinedo (Vrije Universiteit Medical Centre, Amsterdam, Netherlands), who have carried out a dose-finding study with BNP7787, confirm that the compound is tolerated well and that it shows promising efficacy. "BNP7787 has the potential to act as a protective agent against dose-cumulative neurotoxicity from Taxol and cisplatin, without interfering with the chemotherapeutic activity", says Boven. The use of supercomputer engineering to design of compounds by selecting favourable pharmacological characteristics that act against specific targets is, she adds, "extremely elegant". Both Boven and Pinedo welcome the novel design approach being pioneered by Hausheer. "The use of supercomputer technology in drug development should lead to the discovery of many lead compounds in the near future", predicts Boven.

Kathryn Senior

CCI-779: a new targeted anticancer agent

A novel anticancer drug, CCI-779, has shown promise in a series of phase I studies, the results of which were presented at the European Society of Medical Oncology conference (Hamburg, Germany; Oct 13 – 17).

The rationale for developing this anticancer agent came from studies into the mechanism of action of a well-known immunosuppressive agent, rapamycin. This drug was found to target a key component of a novel signalling pathway, called mTOR protein kinase. Preclinical research showed that CCI-779, a derivative of rapamycin, binds mTOR and inhibits the downstream pathway effects, leading to cell growth arrest in the G1 phase of the cell cycle. The mTOR pathway can be hyperactivated by mutation or deletion of the *PTEN*

In a phase I dose-escalation study in France, 21 patients with advanced solid tumours were treated with 7.5 – 220 mg/m^2 CCI-779, given intravenously once a week for 6 months. The maximum tolerated dose has not yet been reached, and toxic effects were mild. Eric Raymond (Institut Gustav-Roussy, Villejuif, France) reported that, of the 16 patients evaluable for response, three with renal-cell carcinoma had a partial (one) or minor response (two), which was maintained for 7 months. There were two other partial responses (neuroendocrine tumour and breast cancer) and one stable disease (soft-tissue sarcoma).

Manuel Hidalgo (University of Texas Health Science Center at San Antonio, TX, USA) reported the results of a US phase I study in 51 patients with cell lung cancer, and minor responses or prolonged stable disease were seen in renal-cell carcinoma (three), cervical cancer (one), uterine cancer (one) and soft-tissue sarcoma (three).

Two randomised multicentre phase II trials are underway, one in renal-cell carcinoma in the USA and the second, in breast cancer, is ongoing in Europe. "It also makes sense to investigate the use of CCI-779 in prostate cancer and in glioblastoma, as these tumours have high rates of *PTEN* mutations, and phase II trials in these tumours are being discussed", says Raymond. "CCI-779 is a very specific, targeted agent. It is therefore crucial to analyse the data collected so far so that we can optimise the doses for tumour response, find out which tumours will benefit most, and use tumour profiles