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Novel DNA-binding compounds for cancer therapy

Researchers at the Auckland Cancer Society Research Centre in collaboration with La Trobe University have developed a novel DNA-binding compound with a novel dual mechanism of action and exceptional preclinical anti-tumour activity

The technology

The Auckland Cancer Society Research Centre (ACSRC) has led the world in developing synthetic DNA-intercalating small molecule anticancer drugs. Amsacrine, first synthesised in 1970 and tested in cancer patients in 1978, is still in clinical use but its activity is limited to leukaemias. Subsequent research has aimed to develop new DNA-intercalating compounds with activity against carcinomas. The drugs asulacrine, DACA and XRT1576 have all advanced to Phase I/II clinical trial. Toxicological problems (e.g. phlebitis, local pain at the infusion) in these clinical trials have meant that these drugs have had limited clinical activity. Our scientists at ACSRC sought to overcome this by synthesising a drug with multiple actions and a superior pharmacokinetic advantage, and together with Prof. L. Deady at La Trobe University, Australia, have developed the novel compound SN28049.

SN28049 has a novel dual mechanism of action; firstly acting as a topoisomerase-II poison by inducing double-stranded DNA breaks and induction of apoptosis. In the second mechanism, cells that survive the wave of apoptosis are unable to complete mitosis and cell division, the p53 pathway is induced and a T-cell mediated response is activated leading to tumour regression.

The anti-tumour activity of SN28049 has been shown to be greatly superior in comparison with clinical topoisomerase-directed drugs using the advanced murine Colon 38 adenocarcinoma. In addition, SN28049 has shown promising results in overcoming multidrug resistance mechanisms which limit the efficacy of other compounds.

Applications

Indications include breast cancer, Hodgkin’s disease, lung cancer, soft tissue sarcoma and relapsing ovarian cancer. It can also be regarded for tumours responsive in xenograft studies for Lung and Melanoma.

IP position

- SN28049 composition: Granted patent in NZ, and accepted national phase applications in the US & AU. Pending National-phase applications in EU, Japan & Canada. Refer PCT application filed 5 May 2003 (PCT/AU03/00569)
- Pending convention application in the US for Oral Compositions, use and combinations of SN28049 and closely related analogues

Competitive advantage

SN28049 has the following advantages over current treatments in its class, such as Doxorubicin:

- Outstanding efficacy: massive apoptosis induction and complete Colon 38 tumour regressions at single low doses in vivo
- Accumulates in and has a far longer half-life in tumour tissue than in normal tissue
- Favourable pharmacokinetic profile over other drugs
- Wide tumour spectrum: active in a variety of xenografts of human tumour cell lines, with tumour growth delays of up to 10 days
- Dual mechanism of action
- Active against a multidrug resistant cell line (cross-resistance ratio close to 1)
- Can be administered orally
- Water-soluble, stable, easy to formulate
- Well-defined large-scale synthetic route
The Auckland Cancer Society Research Centre’s success can be attributed to the productivity, novelty and commercial relevance of their work.

Auckland Cancer Society Research Centre

Within the last decade the Auckland Cancer Society Research Centre has taken eight oncology compounds into the clinic, with one registered and four in late stage clinical trials. One of these, AS1404 (DMXAA), has entered Phase 3 trials and was sublicensed from Antisoma to Novartis last year.

Professors Bill Denny, Bruce Baguley (pictured) and Bill Wilson, lead a multi-disciplinary research staff of 80.

Within the Biology Division, there is extensive expertise in oncology, immunology, molecular biology, proteomics, cell and tumour biology including human tumour assays.

The Medicinal Chemistry Division has an impressive track record and cutting edge expertise in the design and synthesis of small molecular kinase inhibitors, vascular-targeting agents, pro-drug therapies, hypoxia-activated cytotoxins and DNA-targeting agents.

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