Chiroscience/BMS MMP inhibitor progress

In February, Chiroscience (Cambridge, UK) announced a collaboration with Bristol-Myers Squibb. The deal, which had been kept under wraps for several months while details were finalized, established research and licensing between the two companies in the area of matrix metalloproteinase (MMP) inhibitors. BMS will licence the worldwide rights to the two lead compounds D2163 and D1927 and in return Chiroscience will receive development milestone payments for all products as well as royalties on sales. The companies have not disclosed an additional access and research fee payable to Chiroscience but did reveal that BMS will gain all rights to new and jointly selected MMP inhibitors in the area of oncology but not for other therapeutic areas.

The MMP inhibitor D2163 was entered into Phase I clinical trials at the start of the year by Chiroscience. This compound is a chiral mercaptoamide putative anticancer drug and will initially be studied in a double-blind, placebo-controlled trial with healthy volunteers to determine its tolerability, safety margins and pharmacokinetics.

D2163 was designed using a promising approach to producing noncytotoxic anticancer agents that should not affect healthy cells. The approach is to look for inhibitors of the enzymes used by cancer cells to induce the surrounding healthy tissue to support their growth. For instance, the proteolytic breakdown of membranes and angiogenesis (the growth of new blood vessels) are essential in tumour growth and metastasis – the spread of tumours – and involve numerous enzymes any one of which might be a potential drug target. The MMPs are one such group of zinc-dependent enzymes thought to play a pivotal role in cancer development by helping tumour cells to spread.

Tumour progression

Researchers originally thought that tumour cells advance simply because the secreted MMPs break down the extracellular matrix that confines them. However, in July last year Gianluigi Giannelli and coworkers (Scripps Institute, La Jolla, CA, USA) discovered that one such protease, MMP2, not only helps break down this physical barrier to movement and growth but actually causes a signalling cascade that increases cellular motility when laminin-5, one of the extracellular proteins, is broken down and recognized by cancer cells [*Science* (1997) 277, 225–228].

Promising outlook

D2163 has demonstrated a favourable preclinical profile according to the company. It is more active in one chiral form, so Chiroscience, which as the company name suggests specializes in chiral technology, will be utilizing this more active isomer in the trials. It is noteworthy that the compound did not demonstrate the unwanted activity associated with joint pain and tendonitis often seen with other related drug leads [for details of other MMP inhibitors see Beckett *et al.* (1996) *Drug Discovery Today* 1, 16–26].

Company CEO John Padfield is confident that the chiral mercaptoamide will be active against numerous types of solid tumour and will, given positive results from the Phase I trial, enter Phase II trials in late 1998. He is unable to reveal what specific cancers might eventually be treatable but other MMP inhibitors have been shown to be active against a variety of cancers including colorectal and ovarian cancers.

A spin-off of the functionality of the compound might lead to its use in other illnesses, because overexpression of MMPs has also been implicated in diseases such as cartilage degradation in arthritis. Thus, D2163 and its preclinical cousin D1927 might find utility other than as anticancer chemotherapy agents.

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