Basic overview
Combretastatin (CA) compounds are microtubule targeting agents with anti-vascular effects which cause extensive cell death of tumours. We are developing a novel series of β-lactam combretastatin analogues that cause apoptotic cell death of tumour cells including those displaying multi-drug resistance and therefore may be useful for the treatment of many cancers.

What Problem does it Solve & Advantages
At present, the leading CA compound is CA-4-disodium phosphate (zybrestat) but the clinical use of CA-4P may be hindered by instability, toxicity and drug resistance. CA-4 can isomerise to an inactive trans configuration hindering its use therapeutically.

The design of our compounds sees the introduction of a β-lactam group to the standard CA-4 structure and this addition locks these compounds in an exclusively active cis configuration. In addition, compounds containing β-lactam pharmacophores have been reported as inhibitors of cathepsins. Many cathepsins such as B, K, L and S are over-expressed in tumours and play a role in metastasis. The dual targeting of both tubulin and cathepsins in tumour cells by these novel CA analogues should greatly enhance their overall anticancer efficacy.

Competitive advantages of our compounds:
• Greater potency
• Greater stability
• Dual activity (targets tubulin and cathepsin activity)

Docking of β-lactam compound CA-Y in the colchicine binding site of tubulin

Possible Applications
Currently nine million new cases of cancer occur annually, and the WHO has estimated that dramatic increases in life expectancy and changes in lifestyle may increase the number of new cancer cases annually by 2020 and the number of deaths to more than 10 million.

Our products are designed to target the oncology market of metastatic disease. The β-lactam group in these novel compounds provides a recognised inhibitor pharmacophore for cathepsins expressed at elevated levels in tumour cells and thus offers an additional target for these drugs.

Technology and Patent Status
Results in our laboratory have demonstrated that these novel CA analogues depolymerise tubulin in an in vitro tubulin assay with similar efficacy to CA-4. They also potently inhibit the growth of human breast carcinoma MCF-7 cells, human chronic myeloid leukaemia K562 cells and human promyelocytic HL60 cells (including those over-expressing multi-drug resistance proteins) with IC50 values in the nanomolar or subnanomolar range.

Furthermore, they elicit minimal toxicity in primary normal mammary epithelial cells. In addition, these novel drugs, due to their β-lactam pharmacophore, inhibit tumour cathepsin activity, which potentially would help to limit tumour metastases. The synthesis sequence for the β-lactam compounds requires a Staudinger type reaction (microwave optimised) with appropriate protection chemistry.

A patent has been filed on the use of these compounds in the treatment of cancer. (TCD PCT/EP09179351.3.)

The opportunity
This technology is available immediately for licensing and/or for collaborative research.

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Docking of β-lactam compound CA-Y in active site of cathepsin K