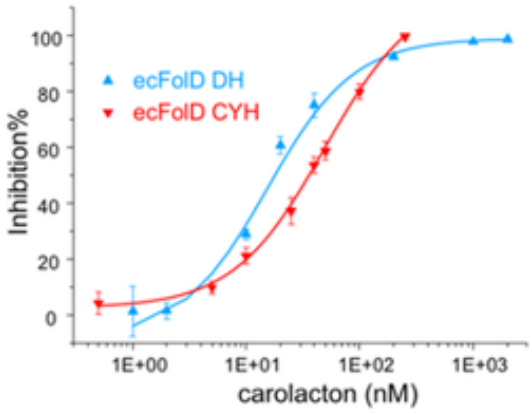
Technology Offer

Carolacton as MTHFD2 inhibitor for cancer therapy

Reference Number 02-00352

Challenge

Cancer diseases still are the second most common cause of death in industrialized countries and the volume of sales for tumor therapeutics is huge. The global market for cancer therapeutics had a volume of more than $ 78 billion in 2015 and is forecasted with more than $ 110 billion in 2020. Although a couple of innovative drugs are in development at present, e.g. targeted approaches such as antibody-drug-conjugates or T-cell therapies, due to side effects, limited responsiveness and resistance issues there is a permanent need for new drugs with a different *mode-of-action*.



Concentration dependent inhibition of the dehydrogenase (DH) and cyclohydrolase (CYH) activity of the purified human mitochondrial MTHFD2 enzyme

Technology

FolD (5,10-methylenetetrahydrofolate dehydrogenase/ 5,10-methyenyltetrahydrofolate cyclohydrolase) is a key enzyme in the C1 metabolism and has a close mitochondrial homologue, MTHFD2, which is highly expressed in cancer-cells, but not in normal adult tissue. Carolacton, which has been discovered to inhibit planktonic growth of *S. pneumoniae* and some *E. coli* strains, is the first natural compound that inhibits FolD/MTHFD2. Even more important to note is that in contrast to almost 70.000 synthetic compounds tested so far, Carolacton is the first inhibitor of MTHFD2 that can enter human cells. Proliferation of different cancer cell lines was inhibited by Carolacton with high efficacy (IC50 between 7-40 nM). No acute toxicity was observed. Since the crystal structure of the target is available and chemical synthesis of Carolacton is established, rational drug design will facilitate lead optimization.

Commercial Opportunity

The technology is offered as a novel scaffold for the development of an anti-cancer drug with alternative *mode-of-action*, for co-development or licensing.

Development Status

In vitro data obtained in different cancer cell lines and primary cells; target validation and *proof-of-concept* in a suitable animal model in preparation.

Patent Situation

Priority was filed in Europe in June, 2017 (EP17174066.5)

Further Reading

Chengzhang Fu et al.2017: The natural product carolacton inhibits folate-dependent C1 metabolism by targeting FolD/MTHFD. *Nature Communications*, 2017, doi:10.1038/s41467-017-01671-5.

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