

Peptides for fighting ovarian cancer developed

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A team of German and Italian EU-funded scientists has designed peptides that can target the protein-protein interface of an enzyme that plays a key part in the DNA synthesis crucial for cancer growth.

With a boost of EUR 1,902,150 of funding as part of the 'Small [ligands](#) to interfere with Thymidylate synthase dimer formation as new tools for development of [anticancer agents](#) against ovarian carcinoma' (LIGHTS) project under the 'Life sciences, genomics and biotechnology for health' Thematic area of the Sixth Framework Programme (FP6), the researchers developed peptides that act by a novel inhibitory mechanism and curb [cancer cell growth](#) in drug resistant [ovarian cancer cells](#).

Writing in the journal *PNAS*, the scientists hope their research will go a long way to helping the some 200,000 women who are diagnosed annually worldwide with ovarian cancer.

In developed countries ovarian cancer is the fifth leading cause of cancer-related deaths in women. Unfortunately, there is a high rate of mortality among ovarian cancer sufferers due to frequent late diagnosis and the rapid rate of [drug resistance](#). Although several clinically important anti-cancer drugs that are widely used in chemotherapy inhibit the enzyme thymidylate synthase, which plays a key role in [DNA synthesis](#), these drugs are also associated with drug resistance. Thus new compounds with different inhibitory mechanisms are required to combat resistance.

According to the Italian and German scientists the answer is

'octapeptides', peptides that specifically target the protein-protein interface of thymidylate synthase, which is composed of two identical polypeptide chains. The peptides stabilise the inactive form of the enzyme, show a novel mechanism of inhibition for homodimeric enzymes and inhibit cell growth in drug sensitive and resistant cancer cell lines.

The researchers have discovered several peptides that inhibit thymidylate synthase by modulating protein-protein interactions. As one of the study's authors Maria Paola Costi from the University of Modena and Reggio Emilia in Italy explains: 'These peptides have sequences from the protein-protein interface of the enzyme and inhibit it by binding to a previously unknown allosteric binding site - that is, a site other than the protein's active site - at the protein-protein interface.'

The team used both experimental and computational approaches to show that their inhibitory mechanism involving stabilisation of an inactive form of the catalytic protein differs from those of protein-protein interface inhibitors reported to date.

Unlike the existing drugs targeting thymidylate synthase, these peptides inhibit intra-cellular thymidylate synthase and cell growth without leading to increased levels of thymidylate synthase protein when administered to [ovarian cancer](#) cells. 'This observation indicates the potential value of these [peptides](#) in overcoming drug resistance problems, although the cellular effects remain to be fully explored,' says another author on the study, Rebecca Wade from the Heidelberg Institute for Theoretical Studies.

The research was led by the University of Modena and Reggio Emilia, Italy and the Heidelberg Institute for Theoretical Studies in Germany. The other organisations involved were the Italian Universities of Siena, Milan and Ferrara.

The overall goal of the LIGHTS project, which ran from 2006 to 2010, was to directly halt tumour progression and the development of drug resistance upon treatment with platinum-derived drugs by inhibiting the protein regulatory function of monomeric TS through small molecule cellular perturbation. The consortium was made-up of both research institutions and small and medium-sized enterprises (SMEs) from France, Germany, Italy, the United Kingdom and the United States.

More information: Cardinal, D., et al. (2011) Protein-protein interface-binding peptides inhibit the cancer therapy target human thymidylate synthase. *PNAS*. DOI: [10.1073/pnas.1104829108](https://doi.org/10.1073/pnas.1104829108)

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