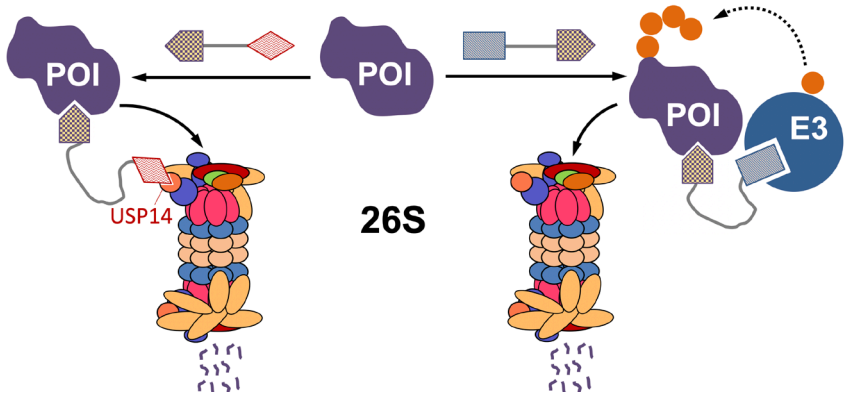
Technology Offer CSIC/IM/080

Novel type of PROTACs directly targeting the proteasome for cancer treatment



Design of a novel proteolytic set of chimeras (26STACs) directed at the degradation of the ceramide transfer protein CERT-1 by the proteasome, in an E3-independent manner, for its use in the treatment of breast cancer.

Intellectual Property

European priority patent application filed

Stage of development

TRL=3. Proof-of-concept tests on several cancer cell lines.

Intended Collaboration

Licensing and/or co-development

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Market need

Proteolysis-targeting chimeras (PROTACs), most acting via E3-ligases/ubiquitin-proteasome system (UPS), have emerged as a promising approach for targeted protein degradation. However, several aspects, such as poor solubility and ubiquitination dependence, limit effective E3-based PROTACs implementation.

On the other hand, CERT is a lipid transfer protein that mediates the transport of ceramide for sphingomyelin synthesis. The ubiquity of sphingolipids in membranes and the key role of ceramide as inducer of programmed cell death, suggests that control of CERT may play a relevant role as enhancer of anti-cancer treatments, such as chemotherapy.

Proposed solution

A new type of small molecule-based proteolytic chimeras, namely 26STACs, has been designed that interact directly with the 26S proteasomal associated factor USP14 to promote degradation of the ceramide transfer protein (CERT-1).

The results obtained so far envisage this approach as a good strategy for targeting crucial proteins for cancer therapy. CERT-1 degradation has been tested in three types of human breast cancer cell lines, one from metastatic carcinoma (MDA-MB-453), one from TNBC (MDA-MB-421) and from a ductal carcinoma (BT-474), at several concentrations.

Competitive advantages

- These chimeras target directly the 26S in an E3-independent manner, thus avoiding ubiquitination dependance for target degradation.
- Potent CERT degradation and proper permeability and toxicity profiles.
- Enhaced efficacy as compared to classical inhibition, requiring less drug to be administered.
- Sensitizing effect in cells exhibiting resistance to HER2-targeted therapies, enhancing action of Lapatinib when jointly administered.