Technology Offer

University of Oulu, Finland (ref. OU15006)

ADP-ribosylation inhibitors for treatment of cancer

Background

Human ADP-ribosyltransferases are targets for therapeutics and it was shown earlier that PARP inhibitors, targeting especially ARTD1 (PARP1), can be used to sensitize BRCA-deficient cancer cells to DNA damage. The research culminated in the approval of the first therapeutic, Lynparza/Olaparib, in 2014. Recently, it has been evident that also other ADP-ribosyltransferases control multiple cellular signaling pathways by affecting protein localization, activity and stability. This has opened up a new avenue for drug discovery, as the ADP-ribosylation of specific target proteins is a key factor in e.g. cancer cell survival and cell death.

Invention

We have discovered a small molecular chemical probe OUL35 for ARTD10 (PARP10) enzyme, which is potent, selective and functional in cell based assays. As ARTD10 is involved in cell death, proliferation and DNA repair the found inhibitor provides a potential therapeutic strategy especially against cancer. We have shown that the compound sensitizes cancer cells to DNA damage though a different mechanism than the more studied ARTD1 (PARP1) inhibitors like Lynparza. The structure-activity relationship studies have shown that the scaffold can also be used to inhibit other human mono-ADP-ribosyltransferases like ARTD8/PARP14 and ARTD15/PARP7, which are also identified drug targets for treatment of hematological cancers.

Field:

- Drug development

Contact

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Status

TRL level: TRL 3

- Tested in cellular models

Patent pending:

- WO2017174879

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Applications

- Treatment of diseases - especially of cancer
- Tools to study biological mechanisms

Benefits

- Selective for mono-ADP-ribosylating ARTD/PARP enzymes
- Confirmed target engagement in cells without cytostatic/toxic effects
- Submicromolar potency in biochemical and cell-assay
- Sensitizes cancer cells to the clinically used chemotherapeutics
- Potential for targeted therapeutics through inhibition of specific ARTD (PARP) enzymes

References

1. **Discovery:** Venkannagari H, Verheugd P, Koivunen J, Haikarainen T, Obaji E, Ashok Y, Narwal M, Pihlajaniemi T, Lüscher B, Lehtiö L. Small-Molecule Chemical Probe Rescues Cells from Mono-ADP-Ribosyltransferase ARTD10/PARP10-Induced Apoptosis and Sensitizes Cancer Cells to DNA Damage. (2016) *Cell Chem. Biol.* **23**:1251-1260.

2. **Derivatives:** Murthy S, Desantis, J., Verheugd, P., Maksimainen, M.M., Massari, S., Ashok, Y., Obaji, E., Nkizinkiko, Y., Lüscher, B., Tabarrini, O. & Lehtiö, L. 4-(Phenoxy) and 4-(benzyloxy)benzamides as potent and selective inhibitors of mono-ADP-ribosyltransferase PARP10/ARTD10. (2018) *Eur. J. Med. Chem.* **156**:93-102.

3. **Derivatives:** Holechek J, Lease R, Thorsell AG, Karlberg T, McCadden C, Grant R, Keen A, Callahan E, Schüler H, Ferraris D. Design, synthesis and evaluation of potent and selective inhibitors of mono-(ADP-ribosyl)transferases PARP10 and PARP14. (2018) *Bioorg. Med. Chem. Lett.* **28**:2050-2054.

Technology Offer

- Available for licensing
- Available for collaboration