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Targeting leukemia through inhibition of purine salvage enzymes

https://www.iocbtech.cz/project/targeting-leukemia-through-inhibition-of-purine-salvage-enzymes/

INHIBITING PURINE NUCLEOSIDE PHOSPHORYLASE TO TREAT T-CELL LEUKEMIAS – A VIABLE TARGET OR NOT?

Scientists

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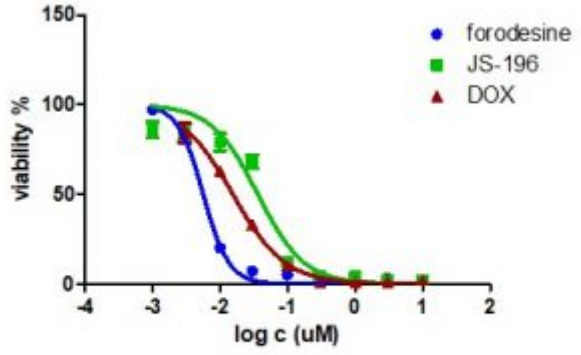
CHALLENGE

T-cell leukemias/lymphomas are a clinically heterogenous group of rare, but often aggressive malignancies. Current treatment options for T-cell leukemias/lymphomas are limited, especially for patients who have relapsed after the first-line treatment. The median overall survival for relapsed peripheral T-cell lymphoma has been estimated at ca. 6 months (Mak 2013; DOI: 10.1200/JCO.2012.44.7524)

Purine nucleoside phosphorylase (PNP) is a ubiquitous enzyme required for purine metabolism. T-cell proliferation is known to be dependent on the purine nucleotide PNP enzyme activity. Thus, effective PNP inhibition could be beneficial in conditions characterized by malignant T-cell growth. The first and so far only marketed PNP inhibitor, forodesine, is currently available only in Japan (as of Jan 2021, brand name Mundesine).

TECHNOLOGY

We have developed novel potent inhibitors of the human PNP (IC_{50} < 100 nM). Our best compounds show selective and efficient cytotoxicity in multiple standard leukemia cell lines, including CCRF-CEM (human lymphoblastic leukemia), MOLT-4 (acute lymphoblastic leukemia, T lymphoblasts), and Jurkat (acute T-cell leukemia, T-lymphocytes), as well as in patient-derived cell lines. No significant cytotoxicity in non-leukemic cell lines (healthy human peripheral blood mononuclear cells, HepG2, HeLa) has been observed. The compounds are well tolerated *in-vivo* (tested up to 10 mg/kg i.p. in mice).



	forodesine	JS-196	DOX
IC50	0.005662	0.03634	0.01548

Fig. 1: Cytotoxic activity of the compounds in CCRF-CEM T-lymphoblastic cell line. Data are expressed as IC_{50} values indicating the concentration of a compound needed for 50 % inhibition of cell growth. Doxorubicin (non-PNP inhibitor) is shown for reference.

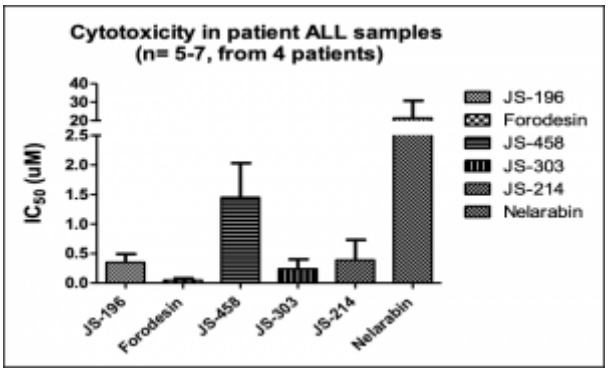


Fig. 2: *In-vitro* cytotoxic activity of the compounds towards T-ALL blasts isolated from the patients.

COMMERCIAL OPPORTUNITY

This project is offered for collaboration/co-development.

DEVELOPMENT STATUS

The project is in the preclinical/lead optimization phase.

PATENT SITUATION

PCT application submitted (PCT/CZ2020/050085)