

Photoisomerizable derivatives of dihydrofolate reductase inhibitors

Market sector: nanomedicine, biotechnology

Type of opportunity: licensing and/ or co-development

Scope of the problem

The dihydrofolate reductase (DHFR) is an enzyme which reduces dihydrofolic acid to tetrahydrofolic acid, using NADPH as the electron donor (reduced form of nicotinamide adenine dinucleotide phosphate). Tetrahydrofolic acid is used for the de novo synthesis of purines, thymidylc acid, and certain amino acids. Because tetrahydrofolic acid is the active form of folate in humans, inhibition of DHFR can cause functional folate deficiency. However, as folate is needed by rapidly dividing cells to make thymine, this effect may be therapeutic.

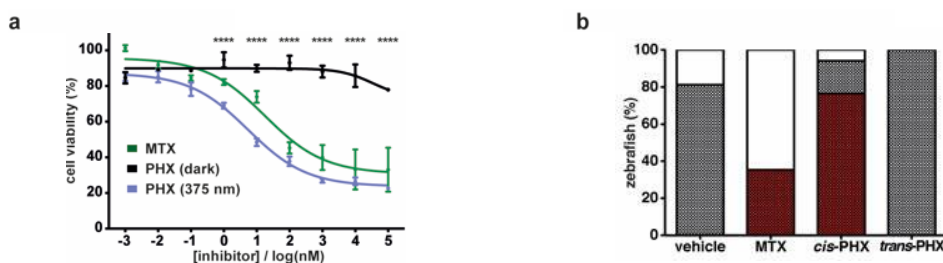
Particularly, these inhibitors can be used as antiproliferative agent due to its inhibitory effect of cell divisions, such as for example in cancer chemotherapy because they can prevent cancer cells from dividing, and also in the treatment of other psoriasis, rheumatoid arthritis, inflammatory diseases of the digestive tract because they can also prevent normal cells from dividing.

There are already existing known compounds used as antimetabolites of the antifolate type which competitively inhibits DHFR, however, serious adverse effects have been reported for these active ingredients. Therefore, from what is known in the art it is derived that there is still the need of providing an inhibitor of the DHFR in which the side effects are reduced.

Patient need addressed: Psoriasis

Our innovation:

- Development of a new light regulated, target-specific antiproliferative compound (PHX)
- PHX is based on an antiproliferative drug approved against psoriasis
- In vitro studies show inhibition of enzymatic activity and arrest of cell growth under illumination at nanomolar PHX concentration
- No antiproliferative effects are observed in the absence of light for a wide range of concentrations (fig. a)
- In zebrafish larvae, the inactive PHX form behaves as the control, whereas light-activated PHX shows effects equivalent to a reference antiproliferative (MTX, figure b).



Competitive advantages: First-in-class compound in this market segment. This approach can address many limitations of classical PDT (photodynamic therapy), which is based on the chemical cytotoxicity of photogenerated species. PHX can be activated locally using clinically-approved PDT lamps. Low side-effects if taking inactivated PHX and only activating it in the skin.

Market size/ opportunity: Psoriasis is a chronic immune-mediated skin disorder that affects about 2-3% of the population worldwide. Plaque psoriasis, the most common form, affect about 80- 90% of patients with psoriasis. The global psoriasis market generated revenues worth US\$7.49 billion in 2014. The top five products accounted for 82% of the market value. The psoriasis market is projected to reach \$9.02 billion by 2019 (with 2014-2019 compound annual growth rate (CAGR) of 3.8% (IMS Midas, IMS Health)).

Intellectual property

European patent application EP17382894.8 (December 12, 2017)

International patent application PCT/EP2018/086233 (December 20, 2018)