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Novel anti-inflammatory compounds

https://www.iocbtech.cz/project/novel-anti-inflammatory-compounds-2-2-2-2/

Scientists

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CHALLENGE

IN-VIVO MODEL OF ULCERATIVE COLITIS IN MICE

Example of substituted pyrimidines efficacy in DSS induced colitis in mice:

WQE-134 (in green) showed substantial mitigation of the inflammatory symptoms. WQE-134 in 10 mg/kg dose was superior to sulfasalazine and/or mesalazine in much higher doses. The efficacy was measured by the Disease Activity Index (DAI) combining the length of the colon, bleeding, stool consistency and loss of weight and by histology evaluation.

Ulcerative colitis or rheumatoid arthritis are diseases causing chronic inflammation (either in the colon or in joints), which (in the long term) stays behind tissue destruction resulting in pathological changes, pain and loss of tissue function. Due to unknown ethiology of both diseases, selective treatment is highly problematic. The huge rheumatoid arthritis drug market (18 B USD) is dominated by TNF-alpha inhibitor drugs (mainly anti-TNF-alpha antibodies) which are able to help patients but they are expensive and not easy to use. Moreover, in the case of ulcerative colitis, there is currently no cure available other than surgically removing affected colon tissue. Therefore, effective and non-toxic drugs belonging to a group of small molecules are highly needed either in ulcerative colitis or rheumatoid arthritis treatment. Novel pyrimidine derivatives were identified among promising anti-inflammatory drug candidates.

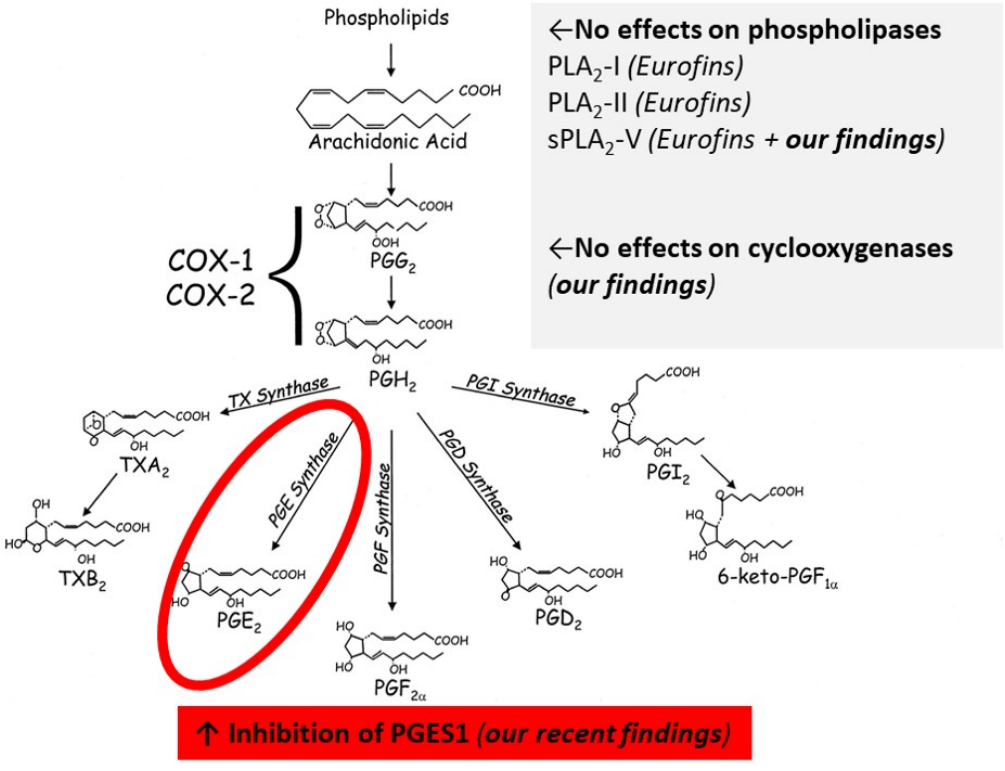
TECHNOLOGY

A library of about 1000 novel pyrimidine derivatives has been prepared and tested for inhibition of prostaglandin E2 (PGE2) production using potentiated (LPS) mouse peritoneal macrophage model.

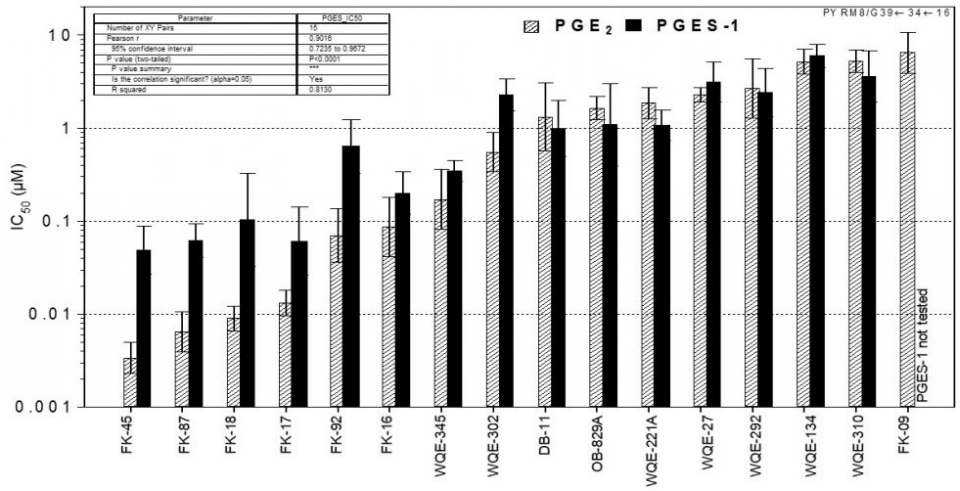
The tested compounds inhibit the production of prostaglandin E2 preferentially by inhibiting the PGES1 synthase. This is based on the evidence of a correlation between PGE2 inhibition and PGES1 inhibition.

We have also observed a small shift in the level of cytokines and nitric oxide (NO) after-treatment of the LPS potentiated macrophages by the pyrimidines. This may additionally play a positive role in the mitigation of the inflammatory process.

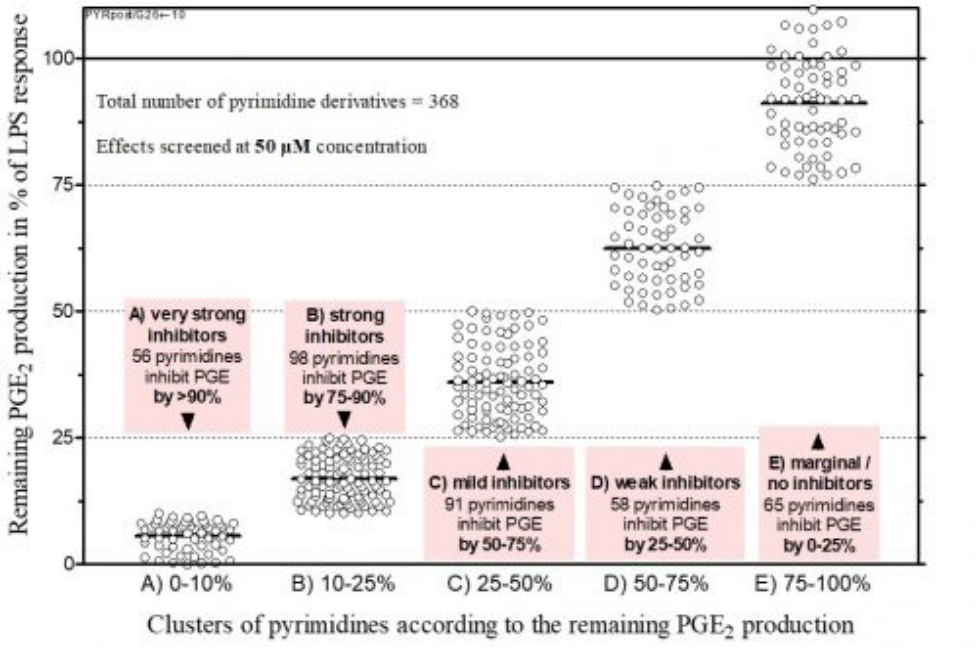
Mode of Action – inhibition of the prostaglandin PGE2 inflammation response by PGES1 synthase inhibition



Mode of Action – inhibition of the prostaglandin PGE2 correlates with PGES1 inhibition

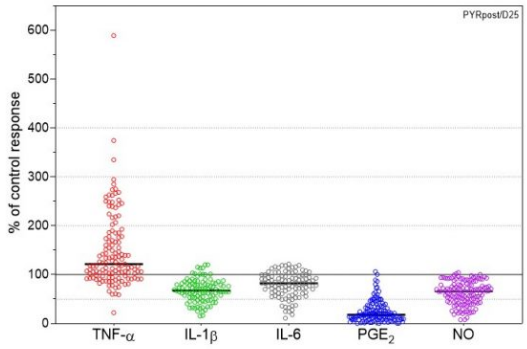


Pyrimidine derivatives are inhibitors of PGE2 production (compounds listed here are not cytotoxic!)



In vitro production and determination of PGE2. Mouse peritoneal cells were cultured (2×106/ml) in presence of LPS (10 ng/ml) and concomitantly added pyrimidines. The supernatant concentration of PGE2 was determined by ELISA (RDSystems) after 5 h of culture.

Mode of Action – slight effect on cytokines inflammation response was observed.



	PGE_2	NO	TNF-α	IL-1β	IL-6
Number of values	131	131	131	106	103
Minimum	0.0370	7.78	22.1	15.2	11.2
25% Percentile	8.71	43.6	97.1	52.7	62.7
Median	18.0	65.6	122	67.2	82.3
75% Percentile	35.0	79.7	178	82.3	97.9
Maximum	107	104	589	120	122
Range	106	96.6	567	105	111
10% Percentile	3.81	25.4	84.9	33.4	40.7
90% Percentile	53.2	93.1	252	101	112
Mean	25.1	62.3	148	67.4	79.0
Std. Deviation	21.8	23.7	75.9	23.0	25.1
Std. Error of Mean	1.91	2.07	6.64	2.23	2.48

Effects of pyrimidines (50 µM) on the secretion of cytokines TNF-a (131 compounds), IL-1b (106 compounds) and IL-6 (103 compounds). For comparison, the effects on PGE2 and NO production are shown. System: mouse peritoneal cells stimulated with LPS and cultured 5 hrs. The concentration of cytokines was determined by ELISA.

COMMERCIAL OPPORTUNITY

The IBD market is about USD 10 bn. and the rheumatoid arthritis market is about USD 18 bn.

DEVELOPMENT STATUS

Early preclinical stage, *in vitro* and *in vivo* testing. Optimization of the lead structure and target validation is proceeding.

CATEGORIES

Anti-inflammatory drugs, auto-immune diseases

PARTNERING STRATEGY

Co-development or out-licencing.

PATENT SITUATION

EP and US patents with a priority date in Feb 2011 were granted:

US 8,883,798 B2

EP 3 195 867 B1

PCT application with priority May 2017 in the process: WO 2018/215003 A1

A new patent application is to be submitted after the lead optimization cycle will be finished.

IP OWNERS

- Institute of Organic Chemistry and Biochemistry of the CAS
- Institute of Experimental Medicine of the CAS

KEYWORDS

Inflammation, IBD, Ulcerative Colitis, Crohn, Rheumatoid Arthritis, Pyrimidines, Prostaglandin E2, PGES1 inhibition

CATEGORIES

Anti-inflammatory drugs, auto-immune diseases