SELECTED OPPORTUNITIES IN ONCOLOGY

Enhancement of 5-Fluorouracil Cytotoxicity by Pyridoxal 5'-Phosphate and Folinic Acid in Tandem(BIO17660)

Product factsheet

Preclinical

Product:

- a B6 vitamer in combination with 5-Fluorouracil and folinic acid.

Rational / POC:

- In tumors,levels of naturally occurring pyridoxal 5'-phosphate (PLP) are too small to allow conversion of tetra hydro pteroylglutamate (H4PteGlu) into methylene tetra hydro pteroylglutamate (CH2-H4PteGlu) in amounts required to improve inhibition of thymidylate synthase by 5-fluorouracil (FUra) through ternary complex stabilization

- Synergistic cytotoxic interaction of FUra with folinic acid and PLP was demonstrated in two human colorectal carcinoma cell lines (HT29 and L1210 cells).

- Murine studies of parenteral administration of pyridoxamine in high doses showed that intracellular PLP is augmented to levels close or greater than the Kd reported for binding of cofactor to serine hydroxymehyl transferase, which suggests that modulation of the fluoropyrimidines by vitamin B6 could be achieved *in vivo.*

Patent and publication:

- **Enhancement of 5-Fluorouracil Cytotoxicity by Pyridoxal 5'-Phosphate and Folinic Acid in Tandem.**

  Machover D, Goldschmidt E, Mollicone R, Haghighi-Rad F, Desterke C, Gaston-Mathé Y, Saffroy R, Boucheix C and Dairou J. **J Pharmacol Exp Ther. 2018 Aug;366(2):238-243.**

- **Patent:** *Methods and Compositions for treating cancer* EP18305661 30 may 2018.

Proof of concept

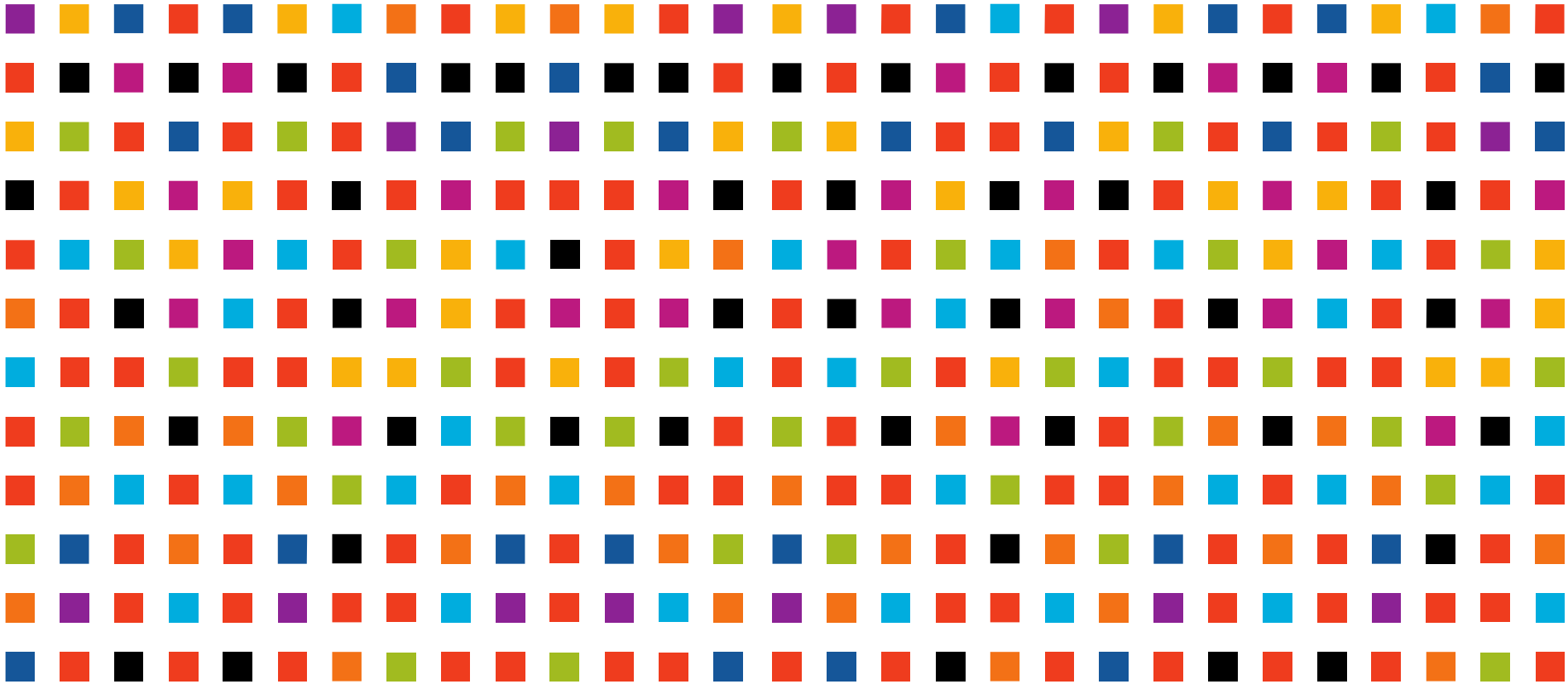
Preclinical

Cytotoxicity of 5-Fluorouracil is increased by Pyridoxal 5'-Phosphate and Folinic Acid in different cellular models

Median–effect parameters and combination indices of FUra as a single agent and in combination with FA and PLP in HT29, HCT116, and L1210 cancer cell lines

Cell Line[a]	Drug[b]	Parameter[c]			Combination Index Value (1.96 S.D.) at Fractional Effect:		
		m	*r*	D_m (IC_{50}) and 95% CI in μM	IC_{25}	IC_{50}	IC_{75}
HT29	FUra	1.236	0.949	1.18 (0.76–1.82)	—	—	—
	FUra-FA	1.082	0.994	0.64 (0.55–0.74)	—	—	—
	FUra-PLP	0.883	0.960	0.66 (0.44–0.99)	—	—	—
	FUra-FA-PLP	0.539	0.989	0.14 (0.10–0.19)	0.18 (0.03)	0.43 (0.06)	1.08 (0.16)
HCT116	FUra	1.23	0.921	1.31 (0.74–2.32)	—	—	—
	FUra-FA	1.21	0.965	0.76 (0.53–1.10)	—	—	—
	FUra-PLP	0.40	0.965	0.46 (0.30–0.71)	—	—	—
	FUra-FA-PLP	0.53	0.941	0.31 (0.16–0.58)	1.43 (0.6)	1.07 (0.24)	1.61 (0.56)
L1210	FUra	1.75	0.969	0.65 (0.40–1.06)	—	—	—
	FUra-FA	1.89	0.990	0.30 (0.20–0.44)	—	—	—
	FUra-PLP	1.635	0.991	0.28 (0.19–0.41)	—	—	—
	FUra-FA-PLP	1.15	0.995	0.08 (0.05–0.11)	—	0.56 (0.06)	0.77 (0.06)

[a]Cancer cells were the human colorectal carcinoma cell lines HT29 and HCT116 and the L1210 murine lymphocytic leukemia.
[b]Cells were grown in customized Dulbecco's modified Eagle's cell culture medium without any B6 vitamer supplemented with 10% fetal bovine serum and were exposed for 72 hours to FUra as a single agent, FUra and FA (20 μM), FUra and PLP (160 μM), and FUra with both FA (20 μM) and PLP (160 μM).
[c]Median–effect parameters are the median–effect dose (D_m) and a coefficient (m) for shape (sigmoidicity) of the dose–effect curve. The linear correlation coefficient of the median–effect plot (*r*) represents conformity of experimental data to the median–effect principle. Median–effect parameters, combination indices, and calculations of error were obtained with the CalcuSyn v2 Software (Biosoft).



ANNE.COCHI@INSERM-TRANSFERT.FR

Inserm Transfert - Paris Biopark
7 Rue Watt - 75013 Paris
Tel: +33 1 55 03 01 00 / Fax: +33 55 03 01 60
www.inserm-transfert.fr