

PAICS Inhibitors for Cancer Cell (cell growth and/or metastasis)

▶ Asset Overview

Product Type	Small molecule
Indication	Oncology (metastatic cancer)
Current Stage	Lead Identification/optimization
Target(MoA)	PAICS Inhibitors
Brief Description	Potent, selective inhibitor of PAICS, a key enzyme in cancer metabolism
Organization	LifeArc

▶ Differentiation

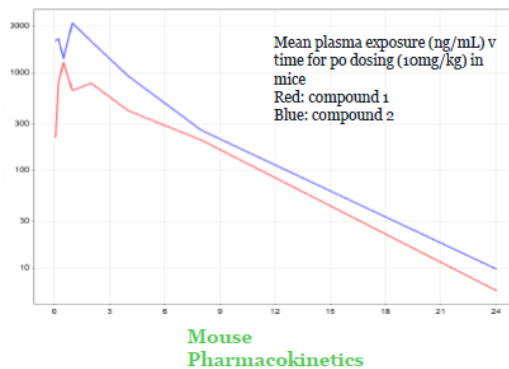
- **Identification of PAICS as a novel cancer target**
 - PAICS is a bifunctional enzyme involved in the de novo purine biosynthesis pathway
 - Rapidly dividing cancer cells have higher metabolic needs than normal cells, which grow more slowly
 - Metabolic study confirmed a dose dependent decrease in AICAR/SAICAR and accumulation of the precursor AIR consistent with cellular IC50 values
- **PAIC mRNA is upregulated in various tumor type**
- **Knockdown of PAICS inhibits proliferation and migration of cancer cell**
- **PAIC inhibitors have a potent cytostatic effect**

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► Key Data

Discovery of small molecule PAICS inhibitors

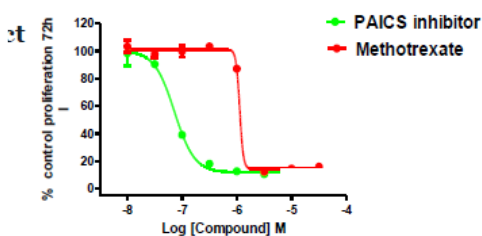
	Biochemical IC50 (nM)	Cell IC50 (nM)	Average LogD	Kin Sol (μ M)	Mouse t1/2 (po)	Mouse Clint (mL/min/kg)	Mouse Bioavailability (%F)
Compound 1	11.5	180	1.3	218	3.2	35.0	97*
Compound 2	3.4	75	1.6	224	3.1	15.0	73



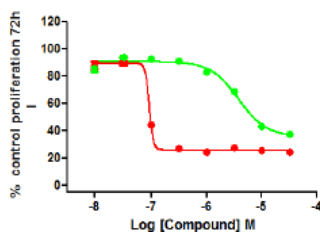
Compounds show good potency and good PK properties in vivo.

Key compounds are tolerated well in mice (14 day study).

Profiling in breast cancer cells



MDA-MB-231 TNBC cell line
aggressive, metastatic 'relatively methotrexate resistant'



Normal human mammary epithelial cells

In breast cancer cell lines they inhibit:

- 2D growth
- anchorage-independent 3D growth
- migration

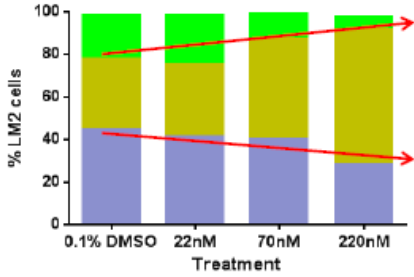
PAICS inhibitors outperform existing anti-metabolite methotrexate in breast cancer cells, sparing normal human mammary epithelial cells

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Effects of PAICS inhibitors on cell cycle

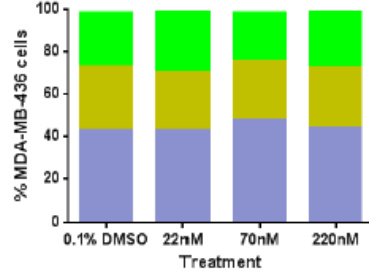
PAICS Sensitive Cell Line

LM2 wt cells with MRT00252040



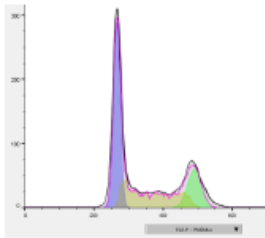
PAICS Resistant Cell Line

MDA-MB-436 cells with MRT00252040

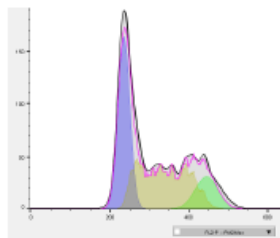


72h incubation with PAICS inhibitor compound MRT00252040

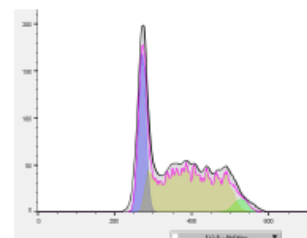
DMSO Control



70nM MRT00252040



220nM MRT00252040



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► Intellectual Property

Patent No.	PCT-GB2017-053821
Application Date	2017.12.19
Status	Application Pending
Country	AU, CA, CN, IN

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