LifeArc

PAICS Inhibitors for cancer cell growth and/or metastasis

Non-confidential summary

PAICS Programme Summary

Project Aim	**To develop first in class cancer therapeutic agent that inhibits PAICS**
Target Class	Enzyme (carboxylase/synthetase)
Therapeutic Area	Cancer (growth and/or metastasis)
Modality	Small molecule
Current Status	Lead series established
Competitive Edge	Potent, selective inhibitor of PAICS, a key enzyme in cancer metabolism
IPR	PCT/GB2017/053821, and PCT/GB2017/053822, filing date 19/12/2017
Offering	Licence or collaboration for preclinical / clinical development

Identification of PAICS as a novel cancer target

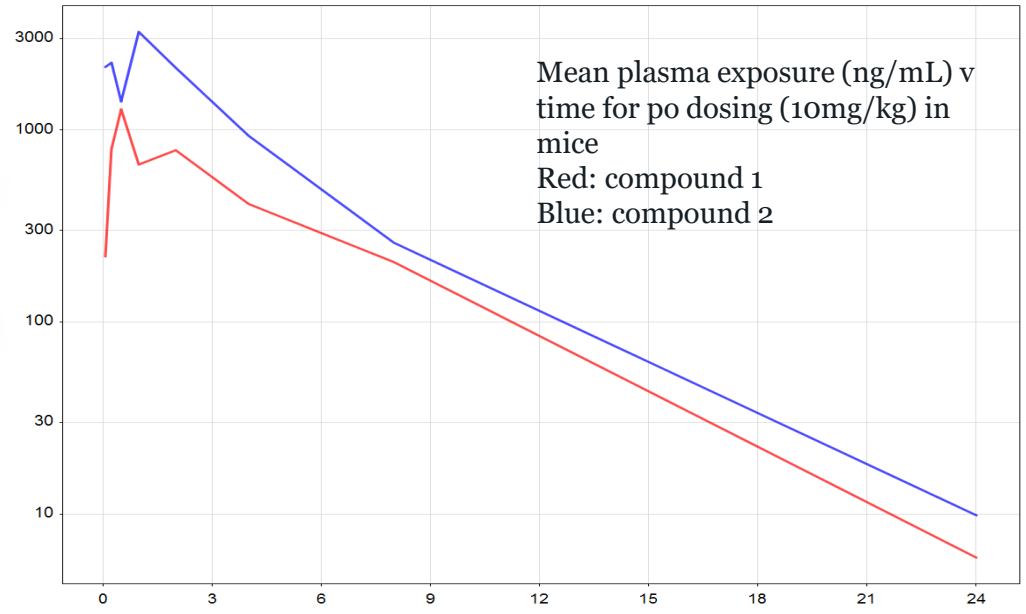
- **PAICS identified as a novel target in breast cancer growth and metastasis** by our collaborator, Daniel Peeper, from the Netherlands Cancer Institute
- **Fra-1** was identified as the most upregulated gene (50-fold) during the experimental acquisition of a metastatic phenotype in breast cancer
- Depletion of **9 genes** strongly inhibited tumour growth and metastasis, one of which was PAICS

- 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
- Normal cells can utilise a salvage pathway to obtain purine, whereas cancer cells are dependent on *de novo* purine biosynthesis
- **Potential therapeutic window** via targeting PAICS

Discovery of small molecule PAICS inhibitors

- LifeArc developed a biophysical assay and carried out fragment screening of PAICS
- Follow up medicinal chemistry was carried out on hits to obtain **highly potent, bioactive PAICS inhibitors**
- Compounds show good potency and good PK properties in vivo
- Key compounds are tolerated very well in mice (14 day study)
- Composition of matter IP has been filed and 2 PCT applications will publish in June 2018

	Biochemical IC50 (nM)	Cell IC50 (nM)	Average LogD	Kin Sol (µM)	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



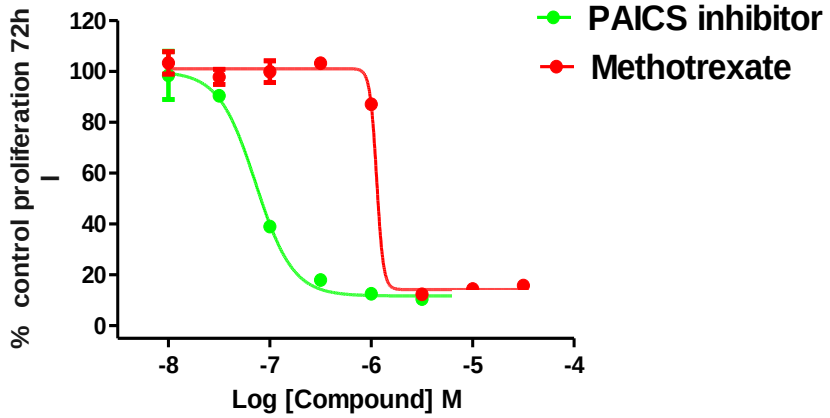
Mouse Pharmacokinetics

Profiling in breast cancer cells

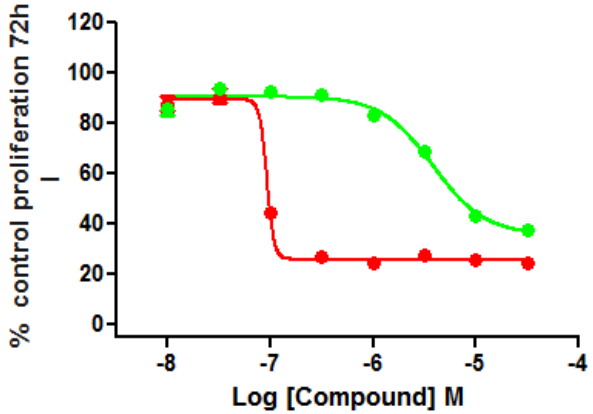
- **PAICS inhibitors have a potent cytostatic effect**

- 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



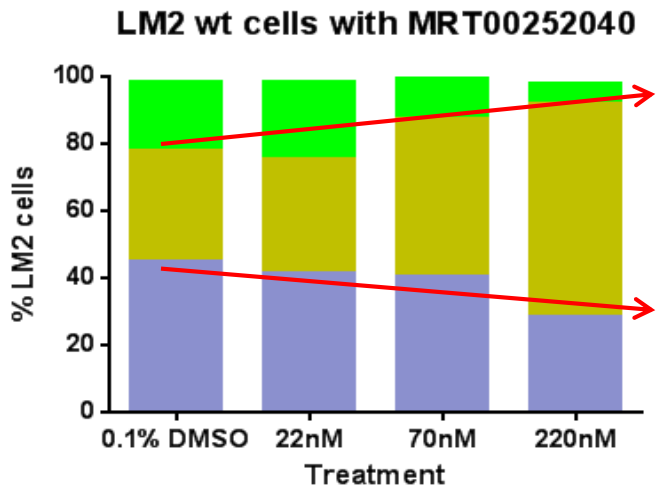
MDA-MB-231 TNBC cell line
Aggressive, metastatic 'relatively methotrexate resistant'

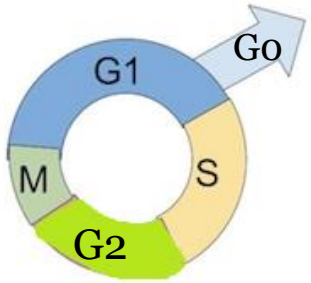


Normal human mammary epithelial cells

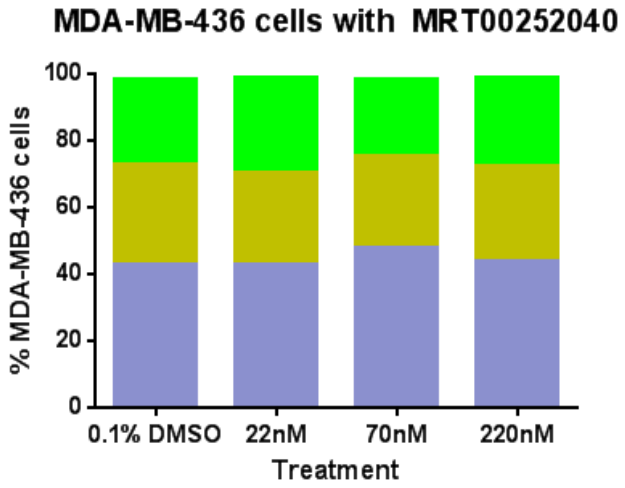
Effects of PAICS inhibitors on cell cycle

PAICS Sensitive Cell Line



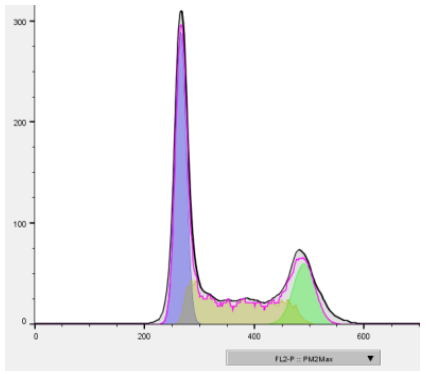


PAICS Resistant Cell Line

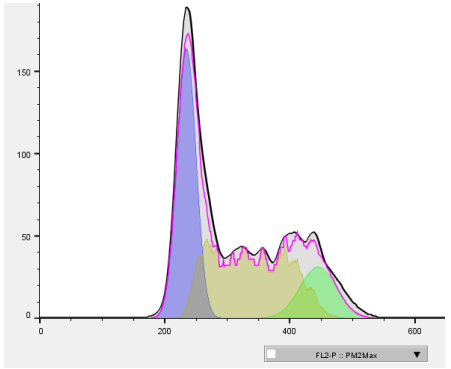


72h incubation with PAICS inhibitor compound MRT00252040

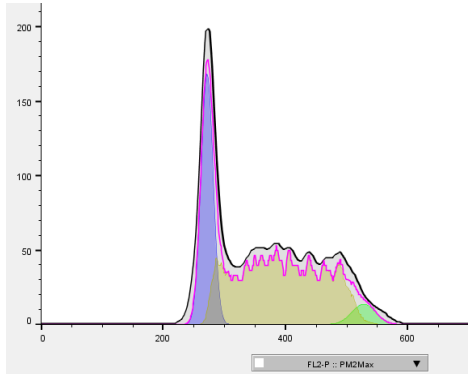
DMSO Control



70nM MRT00252040



220nM MRT00252040



Summary and Areas for Development

PAICS is a novel therapeutic target for cancer and other proliferative disorders

- Targeting PAICS may have potential in a number of different cancer indications
- We have generated novel, potent inhibitors of PAICS
- Inhibitors have on-target activity and demonstrate phenotypic effects
- Inhibitors are tolerated *in vivo* and have suitable PK to enable *in vivo* proof of concept studies
- We continue to work with academic partners to find preferred indication for translation

We are new seeking a commercial partner to explore the potential of these novel inhibitors further

- We can share additional data under CDA such as:
  - Details of *in vivo* studies
  - "Pull-down" data demonstrating high selectivity
  - Kinase profile data
  - Details of bioinformatics studies which demonstrate that our PAICS inhibitor occupies the same therapeutics space as Pemetrexed
  - Potential for PAICS inhibition as a complementary therapy alongside mTOR inhibitors (e.g., everolimus)