Science Bridges China Research Profile

Name: **Klaus Pors**

Position: **Lecturer in Medicinal Chemistry**

Institute/division: **Institute of Cancer Therapeutics (ICT)**

Email: **k.pors1@bradford.ac.uk**

Tel: **+44-(0)1274236482**

SUMMARY OF MY RELEVANT RESEARCH AREAS:

Synthetic & Medicinal Chemistry as Applied to Drug Discovery

适用于药物发现的合成和药物化学。

Primary Research interests:

(i) *Development of Prodrugs Targeting CYP450s for Tumour-Selective Activation*

We have identified several classes of novel *seco*-chloromethylpyrroloindolines as prodrug pharmacophore (Figure 1) and have shown a prototype agent ICT2700 to be active in CYP1A1 transfected cells and is able to significantly delay CHO1A1 but not CHOwt xenograft growth *in vivo.* This work also promises the development of a platform technology whereby the metabolic activation of a selected chloromethylindoline can be matched to a specific CYP. As such, our approach will not only greatly improve the therapeutic index of antiproliferative chemotherapy by circumventing or minimising off-target side effects in normal tissue but also addresses the promise of patient specific therapy.

(ii) Development of Hypoxia-Activated Prodrugs

Solid tumours make up more than 90% of all human cancers and can be considerably less oxygenated than normal tissues, which has been associated with resistance to radiotherapy and chemotherapy in the clinic. The importance of cell killing in those regions of tumours with low oxygen tension (hypoxia) is crucial if cancer is to be effectively treated. Drug treatment failure of solid tumours in the clinic is likely to occur because hypoxic cells divide less rapidly (if at all) than those that are fully oxygenated. The difference in normal tissue and hypoxic tissue can be exploited by designing drugs that are cytotoxic only to cells with a very low oxygen level. The anthraquinone di-*N*-oxide AQ4N (Figure 2), currently in advanced Phase I Clinical trials in the U.K. & the US, is being developed as an adjuvant agent that is used in combination with radiotherapy or chemotherapeutic agents predominantly active against oxic cells. We've used the AQ4N concept to develop molecular triggers that can transport a plethora of drugs to target tissue, and therefore can be uniquely employed as molecular delivery devices.

(iii) Development of Molecular Triggers

The project concerns the synthesis of novel molecular triggers which can be used to deliver cytotoxic drugs to malignant tissues to improve therapeutic index. The know-how for the molecular triggers is derived from the two projects described above.

(iv) Development of Molecular Fluorescent Probes

The project concerns the synthesis of novel small molecules such as DRAQ5 (Figure 3) that can be used to target specific macromolecules in live/fixed cells. The ultimate aim is to invent, develop and market novel reagents for use in cell-based research, drug screening and healthcare diagnostics and to expand these markets through the development of complementary detection and screening technologies.

Topics in which you would like to develop collaborative research:

(i) Drug Discovery, (ii) Drug Delivery, (iii) Molecular Fluorescent Probes to Study Live/Fixed Cells

Relevant existing collaborations (academic/clinical/commercial) inside or outside China.

- Development of Prodrugs Targeting CYP450s for Tumour-Selective Activation
  (i) Prof Laurence H. Patterson (ICT, Bradford, UK)
  (ii) Prof. Magnus Ingelman-Sundberg (Karolinska Institute, Stockholm, Sweden)
- Development of Prodrugs of Natural Products
  (i) Prof. Weishuo Fang (Institute of Materia Medica, Beijing, China).
- Interrogation of DNA-drug Binding & Cellular Damage Responses
  (i) Prof. John A. Hartley (Cancer Research UK Drug-DNA Interactions Research Group, UCL Cancer Institute, London, U.K.)
  (ii) Dr. Grant Stewart (University of Birmingham, U.K.)
- Development of Molecular Fluorescent Probes
  (i) Prof Laurence H. Patterson (ICT, Bradford, UK)
  (ii) Prof. Paul Smith and Dr Rachel Errington (Cardiff University, U.K.).

Relevant graphics, figures, pictures:

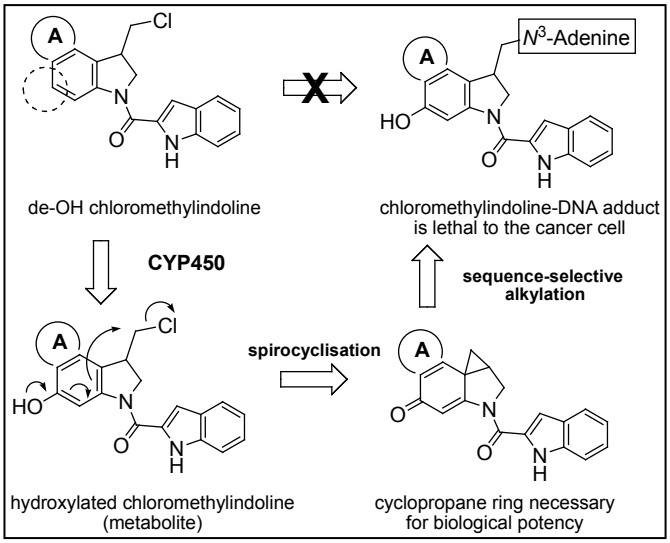

Figure 1: Targeting CYP450s for Tissue-specific Drug Release

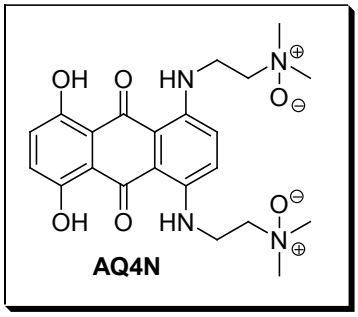

Figure 2: Phase I hypoxia-selective agent, AQ4N.

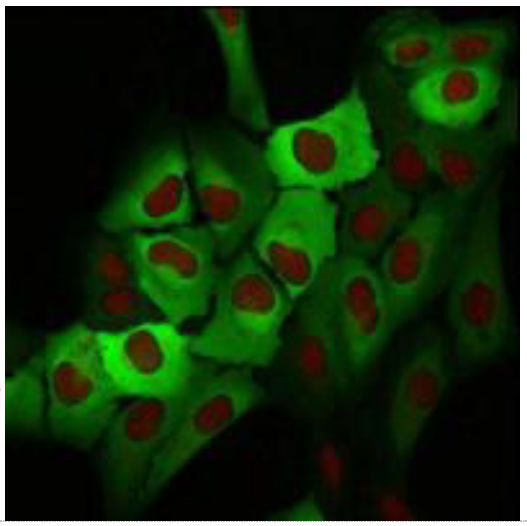

Figure 3: Molecular Fluorescent Probe, DRAQ5

Publications and other outputs relevant to your interest in this programme

- Pors K, Loadman P.M., Shnyder S.D., Sutherland M., Sheldrake H.M., Guino M., Kiakos K., Hartley J.A., Searcey M. and Patterson L.H. Modification of the duocarmycin pharmacophore enables CYP1A1 targeting for biological activity. Chem. Commun., 2011, DOI: 10.1039/C1CC15638A.
- Zhao Y, Fang W.S. and Pors K. Microtubule stabilising agents for cancer chemotherapy. Expert Opin. Ther. Patents, 2009, 19, 607-622.
- Pors K., Shnyder S.D, Teesdale-Spittle P.H., Hartley J.A., Zloh M., Searcey M. and Patterson L.H. Synthesis of DNA directed pyrrolidinyl and piperidinyl confined alkylating chloroalkylaminoanthraquinones; potential for development of tumour-selective N-oxides. J. Med. Chem., 2006, 49, 7013-7023.