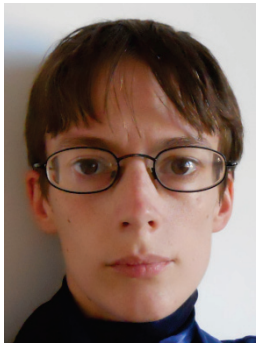
Science Bridges China Research Profile



Name: **Dr Helen Sheldrake**

Position: **Academic Fellow in Medicinal Chemistry**

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SUMMARY OF MY RELEVANT RESEARCH AREAS:

Development of novel molecules to modulate tumour invasion and metastasis, particularly by targeting integrin receptors
Synthetic organic/medicinal chemistry

调节肿瘤的侵袭和转移的新型分子的开发，特别是针对整合整合素受体的开发
有机合成/药物化学

Primary Research interests:

Targeting integrin receptors: The integrin family of transmembrane receptors mediate cell-cell and cell-extracellular matrix interactions and a wide range of cell signalling pathways; changes in integrin expression are frequently seen in cancer. In particular, increased expression of members of the RGD-binding integrin subfamily, particularly those containing the β_3 subunit is associated with progression to invasive tumours. Abnormal expression and activation of $\alpha_{IIb}\beta_3$ and $\alpha_v\beta_3$ in tumours is associated with aggressive disease, metastasis and poor prognosis. Several peptide/antibody antagonists of $\alpha_v\beta_3$ are in clinical trials as anti-angiogenic agents whilst antagonists of $\alpha_{IIb}\beta_3$ have been shown to inhibit experimental metastasis. There is potential for dual antagonism of $\alpha_{IIb}\beta_3$ and $\alpha_v\beta_3$ in cancer treatment; β_3 dual antagonists can prevent tumour invasion by several pathways, blocking the interaction between tumour cells and platelets, or between β_3-expressing tumour cells and ECM in addition to interfering with cell survival signalling pathways resulting in superior efficacy to singly-targeted agents. Extension of this concept to multi-integrin antagonism is likely to improve the activity of agents in preventing angiogenesis and bone metastasis, where other RGD-binding integrins such as $\alpha_v\beta_5$ and $\alpha_5\beta_1$ also play key roles in supporting tumour growth. Using rational design supported by molecular modelling, we have identified novel structures to create a new class of dual β_3 antagonists. We are currently investigating the biological significance of our novel compounds as potential treatments for melanoma and prostate cancer, and potential interactions between this class of compound and other modulators of cancer cell survival signalling.

Organic synthesis: Development of new synthetic methodology, and its application to the synthesis of biologically active compounds. My interest in this area includes the synthesis of rationally designed compounds for medicinal chemistry programmes, and total synthesis of natural products.

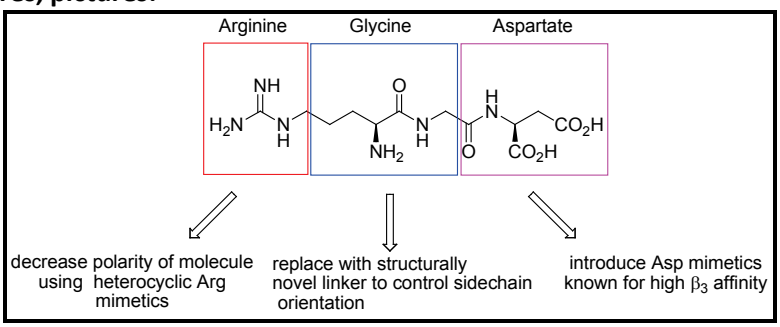
Topics in which you would like to develop collaborative research:

- *New applications of RGD mimetics*
- *Role of integrins in tumour microenvironment-induced drug resistance*
- *Synthesis/semi-synthesis of natural products*

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

Professor Alan Melcher (St James' Hospital Leeds) – novel treatments for melanoma
Dr Janet Brown (St James' Hospital Leeds) – novel treatments for bone metastasis in prostate cancer
Dr Victoria Sherwood (UEA) – cell signalling and kinase mutations in melanoma
Dr Grant Wheeler (UEA) – xenopus embryo assay
Dr Jiwen Zhang (SIMM) - analysis of multicomponent interactions in Cinobufacini TCM

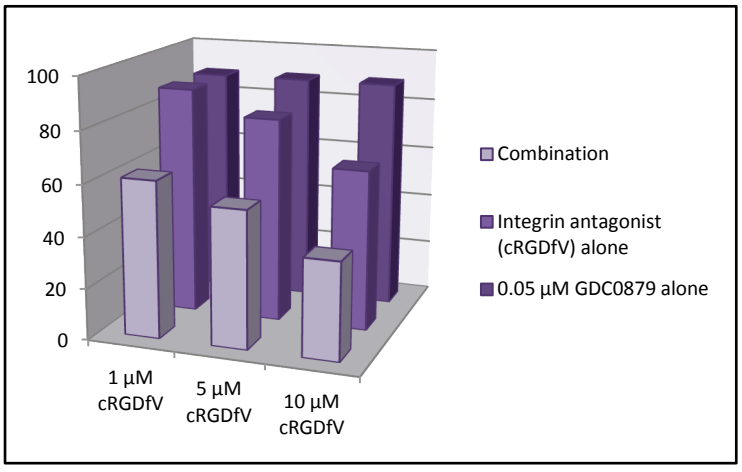
Relevant graphics, figures, pictures:



Design of RGD mimetic integrin antagonists: a library of 80 molecules based around a structurally novel linker unit has been prepared

Compound	$\alpha_v\beta_3$ (Sk-Mel-2)/Fn	$\alpha_{IIb}\beta_3$/Fg
ICT9019 ICT9030	78% (50 µM) 79.1% (50 µM)	6.8% (50 µM) 91.2% (50 µM)
ICT9026 ICT9029	61% (50 µM) 42.5% (50 µM)	20.9% (50 µM) 100% (50 µM)
ICT9055 ICT9064	98% (0.5 µM) 88.5% (50 µM)	50.2% (50 µM) 79.7% (50 µM)
GR144083	41% (5 µM)	65.5% (100 nM)
cRGDfV	83% (5 µM)	-
RGDS	68% (5 µM)	-

Dual β_3 integrin antagonists are identified using cell-based ($\alpha_v\beta_3$) and cell-free ($\alpha_{IIb}\beta_3$) integrin binding assays. The table shows 3 pairs of compounds (parent ester and free acid) compared with controls GR144983 ($\alpha_{IIb}\beta_3$ antagonist), cRGDfV ($\alpha_v\beta_{3/5}$ antagonist) and RGDS (low affinity pan-RGD antagonist). Percentages show inhibition of integrin-mediated adhesion by the stated concentration of antagonist.



Effect of combination therapy with $BRAF^{V600E}$ inhibitor GDC0879 and integrin antagonist cRGDfV on $BRAF^{V600E}$ (Sk-Mel-28) cells. Treatment with cRGDfV plus a non-toxic concentration of GDC0879 significantly increases cytotoxicity.

Publications and other outputs relevant to your interest in this programme

- *RGD-binding integrins in prostate cancer: expression patterns and therapeutic prospects.* M. Sutherland, A. Gordon, S. D. Shnyder, L. H. Patterson, **H. M. Sheldrake**. *Cancers*, **2012**.
- *Function and Antagonism of β_3 integrins in the development of cancer therapy.* **H. M. Sheldrake**, L. H. Patterson. *Curr. Cancer Drug Targets*, **2009**, *9*, 519-540.
- *Synthesis of the originally proposed structure of elatenyne and an enyne from Laurencia majuscula*. **H. M. Sheldrake**, C. Jamieson, S. I. Pascu, J. W. Burton. *Org. Biomol. Chem*., **2009**, *7*, 238-252.