trials of T cell therapy suggest that this is feasible. But he stresses the need not to forget the preliminary stage of all of this research: 'A much larger number of candidate minor antigens must be identified to allow this approach to be tested more broadly', he concludes.

References

1 Zhong, R.K. *et al.* (2002) Sequential modulation of growth factors: a novel strategy for adoptive immunotherapy of acute myeloid leukaemia. *Biol. Blood Marrow Transplant.* 8, 557–568

2 Molldrem, J.J. *et al.* [2002] Overexpressed differentiation antigens as targets of graft-versus-leukemia reactions. *Curr. Opin. Hematol.* 6, 503–508

3 Warren, E.H. *et al.* (2002) Feasibility of using genetic linkage analysis to identify the genes encoding T cell-defined minor histocompatibility antigens. *Tissue Antigens* 4, 293–303

4 Mutis, T. *et al.* (2002) Generation of minor histocompatibility antigen HA-1-specific cytotoxic T cells restricted by nonself HLA molecules: a potential strategy to treat relapsed leukemia after HLA-mismatched stem cell transplantation. *Blood* 100, 547–552

Targeting cell migration

Stephani Sutherland, freelance writer

There are many ways in which cells migrate around the body to carry out essential functions, such as targeted immune reactions, metastatic invasion and angiogenesis. In spite of the diversity of cell type involved, they all use the same basic machinery for motility: the actin cytoskeleton and its associated proteins. Scientists are beginning to develop new ways to identify and study these proteins. Researchers at the University of Illinois in Chicago (http://www.uic.edu/index.html/), for example, have recently identified a compound that stops cells in their tracks in a wound-healing assay [1].

Gabriel Fenteany, lead author of the study, says that the work represents a shift toward therapeutic drugs that target cell motility. But finding an inhibitory compound is only the first step in elucidating the still-mysterious workings of cell movement, and in the even more distant process of developing drugs to exploit it.

Screening for mobility-affecting compounds

The researchers used a screening assay that they report is inexpensive, easy to use, and gives unambiguous results. The assay uses standard 384-well tissue culture plates; a 'wound' is drawn across the confluent cells, and the effects of various compounds on the wound size are then examined. By using Madin-Darby Canine Kidney (MDCK) cells, which maintain a smooth wound edge and migrate as a sheet, Fenteany says that they have eliminated the ambiguity that comes with individually motile cells. The assay enables the screening of 1000 compounds per day, which Fenteany says is 'getting into the realm of respectable high-throughput'. Although that might be high throughput for an individual in an academic lab, there are also commercial operations that screen motility-affecting compounds, such as Automated Cell in Pittsburgh, PA, USA (http://www.automatedcell.com).

Instead of starting with an individual protein, manipulating it, and then measuring its effects on the actin system and motility, Fenteany has taken a different approach: to find compounds that affect motility and work backward to the proteins involved. The newly identified compound, dubbed UIC-1005 (Fig. 1), is similar in structure to a class of antibiotics but has no antibacterial activity. Although both types of compound contain an oxazolidinone ring, says Fenteany, 'it's what's attached to it, and where, that makes all the difference'.

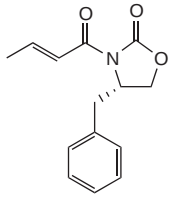

Figure 1. Structure of the compound UIC-1005. Figure provided by Gabriel Fenteany (University of Illinois in Chicago; http://www.uic.edu).

Compound identification

Justin Yarrow, working in the lab of Tim Mitchison at Harvard University Medical School, MA, USA (http://www.hms.harvard.edu/), has used a similar assay to find small molecules that affect motility [2]. Although he agrees that Fenteany's assay is unambiguous, he suggests that it might be an oversimplification to call UIC-1005 a specific inhibitor of cell movement. 'When you're asking for a binary read-out, you have to be asking a very specific question.' One caveat that Yarrow says comes with the assay is that there is a multitude of molecules, from transcription factors to membrane trafficking proteins, that could be affected upstream of actin proteins. 'There are probably billions of compounds that can inhibit wound

 1359-6446/02/$ – see front matter ©2002 Elsevier Science Ltd. All rights reserved. PII: S1359-6446(02)02549-7

healing', he says, but the assay does not identify the target or even the system that is affected by a compound. Ayyappan Rajasekaran, who studies epithelial cells in cancer at the University of California, Los Angeles, CA, USA (http://www.ucla.edu/), agrees that the compound might be affecting processes other than motility. 'MDCK cells divide every 12–13hours. It is important to clarify by specific experiments that the inhibitory effect of this compound is due to inhibition of cell motility and not [of] cell growth'. Yarrow adds that with an all-or-none result, the secondary assay becomes very important to determine the target of your compound. Fenteany's group is now working to identify two candidate molecules that bind UIC-1005.

Fenteany realizes that identification of compounds using a wound assay is a far cry from therapeutic drug development. 'Even if it is very specific…what really happens when you shut down motility?' he asks. 'Those questions have to be addressed.' The best case scenario, says Fenteany, would be 'a magic bullet to bind some protein that is expressed specifically on metastatic cancer cells'. Yarrow points out that therapeutic targets will probably be upstream signaling molecules, which are more likely to be cell specific. 'Compounds that inhibit cell migration through the actin cytoskeleton might very well be more trouble than they are worth.' But there is no doubt that inhibitory compounds will be valuable research tools to determine the roles of the 100 or so proteins that associate with actin, for which there are very few specific inhibitors [3].

Exploiting cell motility

One might envisage an array of applications for compounds that affect motility, from acceleration of wound healing to cell-stopping immunosuppressant drugs. But perhaps cancer is best poised to reap the benefits of a drug that slows cell migration. In the research for anti-cancer therapeutics, says Fenteany, '99% has focused on cell growth', whereas cell motility, 'hasn't been explored as a therapeutic target'. Rajasekaran agrees that motility needs to be exploited in developing cancer treatments. 'The problem of this disease is metastasis, which involves invasion and cell motility. In my mind, therapeutic drugs that target cell motility and invasion will be as critical as drugs that restrict cell growth.'

Although the idea of exploiting cell motility in anticancer therapeutic drugs is not exactly new [4], it is one that has gained increasing momentum in recent years [5,6]. The success of such a strategy becomes more probable with each newly identified molecular player in the realm of cell motility. And understanding those players could just start with a dish of wounded kidney cells.

References

1 McHenry, K.C. *et al.* (2002) A non-antibacterial oxazolidinone derivative that inhibits epithelial cell sheet migration. *Chembiochemistry* 3, 1105–1111

2 Yarrow, J.C. and Mitchison, T.J. (2001) A small molecule approach to cell migration. *Biophys. J.* 80, 1143

3 Peterson, J.R. *et al.* (2001) A chemical inhibitor of N-WASP reveals a new mechanism for targeting protein interactions. *Proc. Natl. Acad. Sci. U. S. A.* 98, 10624–10629

4 McCarthy, J.B. *et al.* (1985) The role of cell adhesion proteins – laminin and fibronectin – in the movement of malignant and metastatic cells. *Cancer Metastasis Rev.* 4, 125–152

5 Otto, T. *et al.* (1999) Tumor cell motility: a novel therapeutic target in bladder carcinoma, experimental and clinical results. *Adv. Exp. Med. Biol.* 462, 469–476

6 Kassis, J. *et al.* (2001) Tumor invasion as dysregulated cell motility. *Semin. Cancer Biol.* 11, 105–117

News in brief

Targets and mechanisms

Leptin: missing link between obesity and breast cancer

The growth factor leptin might be the missing link between obesity and breast cancer in post-menopausal women, say scientists [1].

The findings explain, for the first time, the observation that overweight women often go on to develop breast cancer. The research also contributes to a better understanding of the disease, and will make it easier for susceptible women to be identified and treated as early as possible.

Under the leadership of Margot Cleary, a researcher at the University of Minnesota (http://www.umn.edu/), the group demonstrated that leptin, an adipocyte-derived cytokine, stimulated the proliferation of both normal and cancerous human breast epithelial cells, except that there was a pronounced difference between the two. Whereas normal breast cells proliferated by about 50%, the figure for cancerous cells was closer to 150%.

According to Cleary, 'these findings may explain why weight gain, which is accompanied by higher than expected leptin concentrations, also has been associated with increased breast cancer risk.'

Breast cancer is one of the biggest killers of women today; the World Health Organization (http://www.who.int/en/) estimates that in excess of 1.2 million people worldwide were diagnosed with

 ©2002 Elsevier Science Ltd. All rights reserved. PII: S1359-6446(02)02558-8