In the news

THE STAMPEDE GOES ON

The scramble for the drug trastuzumab (Herceptin) continues unabated for women diagnosed with ERBB2/HER2-positive breast cancer.

Trastuzumab is licensed for the treatment of women with advanced ERBB2-positive tumours, but 3 trials published last October showed that 12 months of trastuzumab and chemotherapy significantly reduced disease recurrence in patients with early-stage disease. Based on these findings, two women in the United Kingdom have taken their local healthcare providers to court in a bid to obtain trastuzumab. One of the women described the initial decision not to provide the drug as "a death sentence" (http://news.bbc.co.uk, 3 March 2006). In New Zealand, women are currently waiting to see whether PHARMAC (the agency that purchases hospital pharmaceuticals) will agree to broaden the use of trastuzumab. However, a PHARMAC spokesperson stated that there are concerns about the safety of trastuzumab (http://www.stuff.co.nz, 19 February 2006).

Indeed, the initial trial did show an increased incidence of heart failure. However, a new trial shows that treating with trastuzumab for just 9 weeks with synergistic chemotherapy lessens the risk of cardiac complications and still significantly improves recurrence-free survival. "These results are pretty good," said Yee Chung Cheng, an oncologist at the Medical College of Wisconsin, but he will "still do 1 year unless there's a much more definitive new study" (http://www.centredaily.com, 6 March 2006).

However, it seems that at least one medical scheme provider is happy to jump the gun. In South Africa, Sam Galliét has been fighting her medical insurance agency to get 12 months treatment with trastuzumab, but she has been offered the 9-week course on the basis of cost. Galliét concludes "this is not the treatment prescribed for me by my doctor. I don't know if this is going to save my life" (http://www.int.iol.co.za, 10 March 2006).

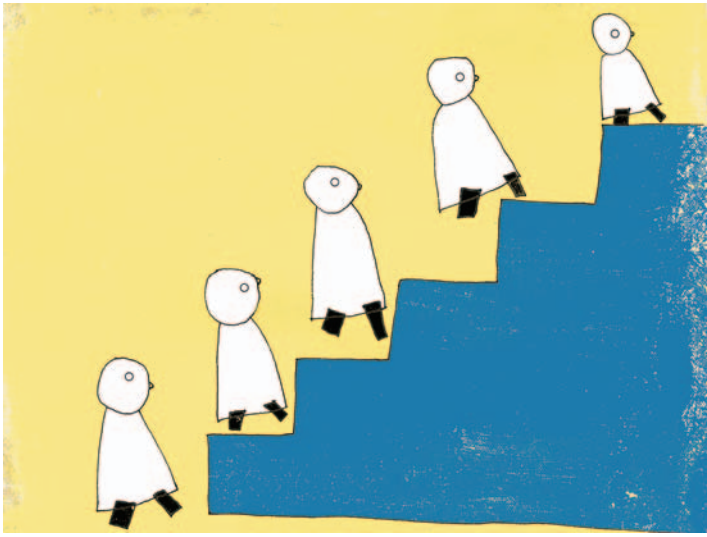
Nicola McCarthy

TUMORIGENESIS

A step towards viral transformation

Viruses are associated with between a third and a quarter of all human cancers, and the mechanisms by which they cause malignancy are varied and complex. Dirk Dittmer and colleagues have used a transgenic approach to investigate the mechanism by which Kaposi-sarcoma-associated herpesvirus (KSHV) leads to the development of lymphoproliferative disease.

KSHV causes, among other diseases, Kaposi sarcoma (a malignant tumour of the connective tissue) and two lymphoproliferative diseases — primary effusion lymphoma (PEL, which often affects the pleural, pericardial and peritoneal cavities) and multicentric Castleman disease (MCD, which causes tumour-like growths in lymph nodes). Previous work by Dittmer and colleagues showed that KSHV-associated tumours express the KSHV latency-associated nuclear antigen (LANA),



a protein expressed in B cells that binds to the tumour suppressors p53 and RB, and to glycogen synthase kinase 3β (GSK3β). This prompted the researchers to investigate the contribution of LANA expression to

LEUKAEMIA

Top-NOTCH

NOTCH1 is aberrantly activated in more than 50% of patients with acute lymphoblastic T-cell leukaemia (T-ALL). Where NOTCH1 functions to transform cells during T-cell maturation has been a matter of considerable debate. Now, Harald von Boehmer and colleagues have more-precisely identified the signalling pathways that cooperate with NOTCH1.

T-cell maturation is a complex process. One of the earliest stages is characterized by lymphocyte precursors that have yet to express a functional pre-T-cell receptor (pre-TCR). An initial set of experiments in mice indicated that NOTCH1 cooperates with the pre-TCR in the generation of T-ALL, as T-ALL did not arise from non-pre-TCR-expressing cells. However, data from a different mouse model indicated that NOTCH1 can induce T-ALL in a pre-TCR-independent manner.

To address this, the authors made a retroviral vector that expresses the intracellular domain of NOTCH1 (ICN1), and infected pre-TCR-negative bone-marrow cells. These cells were then injected into lethally irradiated syngeneic mice. These mice died of T-ALL 9 weeks after transplantation. To examine the requirement for a functional pre-TCR in this process, the authors injected these cells into recombination-activating gene 2 ($Rag2$)$^{-/-}$ mice,

> "pre-TCR signalling might, in combination with NOTCH1 signalling, increase the occurrence of secondary transforming events"

the development of B-cell tumours caused by KSHV.

To express LANA at pathogenic levels, the researchers made mice that were transgenic for LANA under the control of LANAp, the viral KSHV LANA promoter, which is B-cell specific and constitutively active in KSHV-associated malignancies. The transgenic mice expressed levels of LANA mRNA equivalent to the levels found in PEL.

The researchers found that the B cells of the transgenic mice resembled B cells that had been activated by antigen — they were hyperproliferative, focally aggregated and activated. Furthermore, the mice all had benign lymphoproliferative disease, and although transgenic LANA expression itself was not enough to cause complete germinal-centre maturation (this requires activation by paracrine signals and antigen), the authors found that some of the transgenic mice developed large B-cell lymphomas as they aged.

So, the benign lymphoproliferative disease phenotype increased the likelihood of developing B-cell lymphomas — but what other signals are needed for transformation?

Previous studies have shown that LANA expression can increase the probability of cell activation through the Ras–MAPK pathway. For PEL and MCD, other KSHV oncogenes are thought to provide the secondary signals for frank B-cell lymphomas. The results of the present study lead the authors to suggest that continuous antigen exposure could provide the trigger for lymphoma development. They also speculate that co-infection by other pathogens (often seen in AIDS patients) could provide the secondary signal.

As the first animal model of KSHV-dependent B-cell lymphomagenesis, the authors hope that the LANA transgenic mice will help determine the mechanism by which LANA stimulates B cells, as well as identify the secondary stimuli needed for transformation. Possible candidates include the KSHV cyclin-D homologue, which is already known to cause B- and T-cell lymphomas.

Jenny Bangham

ORIGINAL RESEARCH PAPER Fakhari, F. D., Jeong, J. H., Kanan, Y. & Dittmer, D. P. The latency-associated nuclear antigen of Kaposi sarcoma-associated herpesvirus induces B cell hyperplasia and lymphoma. *J. Clin. Invest.* **116**, 735–742 (2006)

which are unable to express a functional pre-TCR. These mice still developed T-ALL, but with slower kinetics and died at 11 weeks post-transplantation. Anti-CD3 antibodies can mimic pre-TCR signalling, and when the authors injected newly transplanted *Rag2*$^{-/-}$ mice with anti-CD3 antibodies, the mice died of T-ALL at 9 weeks, comparable with the wild-type controls.

Further experiments indicated that NOTCH1 signalling is required for the proliferation of immature thymocytes from normal mice. The authors suggest that aberrant NOTCH1 activation might induce increased survival and proliferation of these cells and so increase the likelihood of secondary genetic events that result in T-ALL.

The authors conclude that pre-TCR signalling is not essential for the development of T-ALL, but that pre-TCR signalling might, in combination with NOTCH1 signalling, increase the occurrence of secondary transforming events. Once these events occur however, pre-TCR signalling is no longer required.

Nicola McCarthy

ORIGINAL RESEARCH PAPER Campese, A. F. *et al.* Notch1-dependent lymphomagenesis is assisted by but does not essentially require pre-TCR signaling. *Blood* 28 Feb 2006 (doi:10.1182/blood-2006-01-0143)

Trial watch

A SHORT COURSE MIGHT BE ENOUGH

Amplification of *ERBB2* (also known as *HER2*) occurs in 15–25% of breast cancers, and giving the antibody trastuzumab (Herceptin) with chemotherapy increases survival. In a phase III trial of women with breast cancer, the FinHer (Finland Herceptin) Study investigators have shown that a short course — just 9 weeks — of trastuzumab given concomitantly with docetaxel or vinorelbine is effective in patients with amplified *ERBB2*.

Although survival improves when trastuzumab is given concomitantly with paclitaxel or after chemotherapy for 12 months, there is a risk of heart failure in 1.7–4.1% of women. So, investigators tried a different approach — administering trastuzumab before other cardiotoxic therapies and with potentially synergistic chemotherapy.

A total of 1,010 women with axillary node-positive or high-risk node-negative breast cancer were randomly assigned to receive either docetaxel or vinorelbine. Of these, 232 had amplified *ERBB2* and were further randomized to receive trastuzumab or not to receive it. Nine trastuzumab infusions were administered at 1-week intervals starting on day 1 of the first docetaxel or vinorelbine cycle. All patients received fluoruracil, epirubicin and cyclophosphamide (FEC). Median follow-up times were between 35 and 37 months.

Recurrence of breast cancer or death without recurrence was less common among women treated with docetaxel plus FEC than among women treated with vinorelbine plus FEC, but overall survival was not significantly different. Of 115 patients in the trastuzumab group, 12 had recurrent breast cancer or death without recurrence; in the control group (116 patients) 27 such cases occurred. Overall survival also tended to be better if the patient had received trastuzumab. The most common dose-limiting side effect was neutropaenia and neutropaenic infection, especially in the docetaxel-treated group, so dose reductions were made accordingly. Four patients had cardiac infarctions or cardiac failure — none of these patients had received trastuzumab.

These data need to be confirmed in a larger scale study, but the use of 9-week trastuzumab in this schedule holds promise for reducing the numbers of patient visits, decreasing the numbers of cardiac adverse events, and increasing the cost-effectiveness of breast cancer therapy.

ORIGINAL RESEARCH PAPER Joensuu, H. *et al.* Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N. Engl. J. Med.* **354**, 809–820 (2006)