mouse model of mutant-FLT3-mediated leukaemia, PKC412 treatment completely blocked the development of leukaemia, whereas all of the mice in the placebo group developed fatal disease. Moreover, spleen weights and WBC counts were also significantly lower in the treated mice.

Both of these studies strongly support the idea that FLT3 is potentially a good drug target in AML. PKC412 and CT53518 are now being evaluated in clinical trials for AML, and it seems likely that several other FLT3 inhibitors will also be clinically tested. It will be of considerable interest to compare their efficacies and toxicities, as these are likely to be influenced by the non-FLT3 targets of each drug, which might differ significantly.

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VIRAL INFECTIONS

Exchange control

Exchange is a fundamental process of life. In one type of cellular exchange process, the enzyme thioredoxin and the tripeptide glutathione mediate reduction–oxidation reactions between molecules. Disulphide exchange in one of the molecular domains of the CD4 molecule is required for entry of HIV-1 into T cells, according to new research in the August issue of *Nature Immunology*. This redox change could represent new potential targets for HIV-entry inhibitors.

HIV infection of helper T cells requires the receptor CD4, as well as a chemokine co-receptor. Although co-receptor use varies between virus strains, the use of the CD4 receptor is an almost universal feature of HIV-1 strains. CD4 is a surface membrane protein that is expressed at high levels on helper T cells. The molecule contains four immunoglobulin-like domains — D1 to D4 — of which D1, D2 and D4 each contains an intramolecular disulphide bond. These are formed when the sulphhydryl group of one cysteine residue reacts with that of another cysteine in an oxidation reaction to form a disulphide bridge. An unusual feature of the D2 disulphide bond is its relatively high strain energy compared with the other disulphide bonds, which makes it more prone to reduction to the free sulphhydryl groups.

Hogg and colleagues showed that a fraction of the cell-surface CD4 molecules contained one or more free thiols, and this was due to redox activity of the D2 disulphide bond. Regulation of the D2 redox state seems to be controlled by thioredoxin, which is secreted by T cells. The authors tested whether the redox state of the CD4 D2 domain

was important for HIV-1 entry. To prevent the exchange between the oxidized and reduced forms, the authors used glutathione arsenoxide, which consists of a trivalent arsenical attached to the cysteine thiol of glutathione. Trivalent arsenicals form high-affinity ring structures with closely spaced dithiols, but not with monothiols or dithiols that are spaced far apart. Fixing the D2 thiols in the reduced state by labelling with this agent blocked HIV entry. It seems, therefore, that conformational changes in the D2 domain after reduction/oxidation and/or disulphide-dependent dimerization of CD4 molecules are important for HIV-1 infection of T cells.

Binding of the envelope protein of HIV-1 to CD4, which occurs through the D1 domain, is not affected by the redox state of the D2 disulphide. HIV-1 entry, however, occurs preferentially by means of receptors that are in the oxidized state. Detailed quantification of binding kinetics and avidity of HIV for the different redox forms of CD4 might reveal the explanation for the authors' observations. As well as having potential therapeutic applications for HIV-1 infections, this strategy could be a general approach for other molecules that contain redox-active structures.

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WEB SITES

Hogg's laboratory:
<http://notes.med.unsw.edu.au/resinterests.nsf/sw/9100604>