Alternative models are worth considering if they suggest new experiments; this suggests several. First, it should be possible to replace As by P (and perhaps even N) without a diminished anti-corrosive effect in brass. Second, other non-metal pairs as well as B/nitride, such as C (or Si) with Si (or O), might behave similarly. Third, the solubility of B and As (or P) in brass may depend on each other’s concentration and on the divacancy concentration. Novel quaternary intermetallic compounds of B and As might even be found. Finally, the trick should not work in alloys of metals below group 10 which corrode with a divacancy mechanism if formation of metal boride or arsenide phases competes.

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Figure 1 Effects of neoglycopolymer on human neutrophils. a, Chemical structures of an L-selectin binding epitope on GlyCAM-1 (Ac = acetyl) and the 3',6-disulpho Lex neoglycopolymer. b, Histogram overlay of L-selectin expression by untreated cells (grey) and cells treated with the 3',6-disulpho Lex neoglycopolymer (267 μM or 4 mM on a per saccharide basis; black). c, Histogram overlay of L-selectin expression by untreated cells (grey) and cells treated with the monomeric ligand 3',6-disulpho Lex(Glc)-8-OPr (4 mM) (black). d, Histogram overlay of Mac-1 expression by untreated cells (grey) and cells treated with 10 nM PMA (black). e, Histogram overlay of Mac-1 expression by untreated cells (grey) and cells treated with 3',6-disulpho Lex neoglycopolymer (267 μM or 4 mM on a per saccharide basis; black). Histogram depictions are representative of at least three experiments monitored by flow cytometry using a fluorescein isothiocyanate-conjugated anti-L-selectin antibody or a phycoerythrin-conjugated anti-Mac-1 antibody.

Synthetic ligands point to cell surface strategies

Protein shedding, the proteolytic release of a cell surface protein, can serve a regulatory role by liberating soluble molecules into circulation while decreasing their concentration on the cell surface. We have created a new class of multivalent ligands, ‘neoglycopolymers’, which are designed to promote the proteolytic cleavage of a cell adhesion molecule involved in the inflammatory response, L-selectin. These synthetic ligands induce the release of the extracellular portion of L-selectin by appropriating an endogenous protease; such activities suggest new strategies to generate anti-inflammatory agents and regulate the cell surface.

L-selectin mediates the process of leukocyte rolling, an initial step in the inflammatory response, by recognizing carbohydrate epitopes that are present on endothelial cells. L-selectin is constitutively present on the surface of most leukocytes, but a soluble form is also found in circulation.

The L-selectin ligands that occur physiologically, such as GlyCAM-1 (ref. 4), are mucin-like proteins which contain clusters of O-linked saccharide chains. Such chains could engage L-selectin in multivalent binding at the cell surface. We hypothesized that the clustering of L-selectin, as a consequence of ligand binding, leads to the proteolytic release of its soluble form from the cell.

So we synthesized molecules that, like mucins, present multiple copies of saccharide epitopes on an extended backbone. Such ligands might cluster L-selectin by mimicking either the mucins themselves or the multivalent display of mucin epitopes at the cell surface.

The L-selectin recognition element was based on the disulphated trisaccharide 3',6-disulpho Lewis x (Le x), an analogue of the GlyCAM-1 capping group 6-sulpho sialyl Le x (Fig. 1a). To assemble the recognition elements into a multivalent saccharide array, we used ruthenium carbene-catalyzed ring-opening metathesis polymerization (ROMP) 5, a technique that tolerates multiple unprotected functionalities and can produce polymers of consistent and controllable lengths. We produced synthetic ligands composed of about 15 monomer units, each substituted with the recognition epitope 3',6-disulpho Le x (Fig. 1a).

When we treated human neutrophils with these neoglycopolymers, L-selectin was lost from the cell surface in a dose-dependent manner (Fig. 1b). Soluble L-selectin was detected in the supernatant of treated cells; therefore the decrease on the cell surface was due to shedding.

In contrast, the monovalent ligand 3',6-disulpho Le x(Glc)-8-OPr did not cause L-selectin release (Fig. 1c). And a galactose-substituted oligomer, which does not bind L-selectin, had no effect.

Cellular activators, such as phorbol esters and chemotactic peptides, also induce the shedding of L-selectin; at the same time they dramatically increase the surface concentration of the β2-integrin Mac-1 (CD11b/CD18) (Fig. 1d), a protein involved in the next step of leukocyte...
recruitment to the endothelium.

To determine whether a similar mechanism was associated with neoglycopolymer-promoted L-selectin shedding, we monitored Mac-1 levels in neoglycopolymer-treated cells. Surprisingly, the neoglycopolymer had no effect on Mac-1 expression (Fig. 1e). Moreover, hydroxamic acid-based protease inhibitors, which diminish the activation-induced shedding of L-selectin14, do not prevent neoglycopolymer-induced shedding (data not shown).

The disparity in protease inhibitor activities raises the possibility that different proteases mediate the activation-dependent and independent events. These results indicate that molecules sharing aspects of physiological L-selectin ligands can induce L-selectin shedding, and that the release mechanism is distinct from that occurring following cellular stimulation.

Several unique features characterize neoglycopolymer-promoted shedding of L-selectin. The neoglycopolymer, like other selectin inhibitors, compete with natural ligands for selectin binding by non-covalent and independent events. These results indicate that molecules sharing aspects of physiological L-selectin ligands can induce L-selectin shedding, and that the release mechanism is distinct from that occurring following cellular stimulation.

Proteins that are shed from the cell surface form a diverse group. They include growth factors, cytokine receptors, cell adhesion molecules and leukocyte antigens15. This diversity underscores the potential applications of receptor shedding in altering cellular responsiveness to specific ligands, or promoting responses at distal sites. We have demonstrated the possibility of devising molecules that selectively promote the shedding of L-selectin, suggesting a new strategy for generating anti-inflammatory agents. Because other proteins may undergo ligand-induced shedding, these results have broad implications for the investigation and manipulation of the cell surface and the extracellular environment.

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**Thyroid cancer risk to children calculated**

The Chernobyl reactor accident was followed by a sharp increase in the incidence of thyroid cancer among children and adolescents in Belarus (Belorussia) and Ukraine9,10. Exposure to iodine-131 ($^{131}$I) was responsible for most of the doses that affected the thyroid of these children; however, among evacuees, up to 40% of each dose could derive from other incorporated radionuclides and external exposures8. From the data set compiled after this incident, we estimated the increased risk of developing thyroid cancer after exposure to radioactive iodine. The figure we obtained for most of the affected regions fell within the 95% confidence interval of a previous follow-up of thyroid cancer after external exposures.

In Ukraine, more than 150,000 measurements of $^{131}$I activity in the thyroid were performed from mid-May to mid-June 1986. Collimators shielded against radiation from other parts of the body and from the environment during the taking of these measurements. Background signals were continuously monitored and subtracted from the results.

In a re-evaluation of these measurements8, we reconstructed average thyroid doses due to $^{131}$I exposure for three regions close to Chernobyl — Kiev, Zhytomyr and Chernigov, containing 4,406 settlements (villages or towns) — and for evacuees (Table 1). Dose distributions in settlements with fewer than 12 thyroid measurements were estimated from settlements contributing many measurements by taking into account contamination by caesium-137 ($^{137}$Cs) of the ground, and the settlement’s location relative to Chernobyl1.

For children less than three years old living in contaminated areas, the dose received exceeded that to adults by a factor of five, while among evacuees the child dose was about 20 times greater than that received by adults. Individual doses show large variability, but this contributes only slightly to the uncertainty, of average thyroid dose estimates because of the size of this study. We estimate that a factor of 4 separates the 95% confidence boundaries of average thyroid doses.

For Belarus, deriving $^{131}$I activity concentrations in thyroid is more difficult because here the measurements of $^{131}$I activities in the thyroid were performed with non-spectrometric and uncollimated devices. However, $^{131}$I activity measurements in milk and soil are available16,17. Thyroid doses were assessed for 812 settlements. In Bryansk, the most contaminated region of Russia, 14,000 measurements of $^{131}$I activities in thyroids were performed. Count rates detected with non-spectrometric devices were corrected for the contribution of radio-caesium in the body. Thyroid doses in 602 settlements were calculated by taking into account data on milk and soil contamination7.

Of 264 checked cases from Belarus and Ukraine, western European pathologists approved the thyroid cancer classification in 97% (ref. 8). In southern Ukraine, which we used as a control area, the thyroid cancer incidence among 9 to 18-year-olds increased by 70% from the period 1986–1988 to the period 1991–1995. This probably reflects both greater thyroid surveillance and Chernobyl radiation. In principle there might be a higher screening effect in the contaminated regions. However, the high frequency of metastases (these were found in lymph nodes in 66% of the children operated on in

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**Table 1** Thyroid cancer risk among children born between 1971 and 1986

<table>
<thead>
<tr>
<th>Area</th>
<th>Children (x 10$^6$)</th>
<th>Average thyroid dose (Gy)</th>
<th>Thyroid cancer cases 1991–1995</th>
<th>Observed/expected cases</th>
<th>Excess absolute risk (per 10$^6$ person-year Gy)</th>
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<tbody>
<tr>
<td><strong>Ukraine</strong></td>
<td></td>
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<td>Zhytomyr oblast</td>
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<td>4</td>
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<td>399</td>
<td>0.18</td>
<td>47</td>
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<tr>
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<td>273</td>
<td>0.09</td>
<td>33</td>
<td>6</td>
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<td>Kiev city</td>
<td>581</td>
<td>0.05</td>
<td>67</td>
<td>6</td>
<td>3.8</td>
</tr>
<tr>
<td>30 km zone (evacuees)</td>
<td>20</td>
<td>0.92</td>
<td>12</td>
<td>30</td>
<td>1.3</td>
</tr>
<tr>
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<td>Gomel/Mogilev oblast</td>
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<td>169</td>
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<td>31</td>
<td>9</td>
<td>2.7</td>
</tr>
</tbody>
</table>

a: Expected cases are calculated on the basis of the incidence in southern Ukraine of 4.2 cases per 10$^6$ person-years.
b: An oblast is an administrative region

c: Subarea of the region only

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