

bound form¹. This loop adaptation mirrors the AB loop changes seen in GH between the free (affinity matured) structure, or two distinct bound states^{2,8}. Another notable eccentricity of IFN- γ binding concerns the role of a crucial basic cluster at the carboxy terminus of a long, curving tail; this structure can be modelled to nestle against a conserved acidic patch on the R α carboxy-terminal Ig domain¹, which curiously exists mostly because of an IFN- γ R α -unique³, disulphide-looped chain extrusion¹. The 2:2 IFN- γ :R α structure remains an intermediate, inactive complex in wait of one or two accessory R β molecules¹³ that speculatively dock against respective Ras in the vicinity of the same acidic patch, perhaps engulfing the basic IFN- γ tail¹. This potential R β binding model would also engage the A-C helix faces of each IFN- γ helix bundle and hence locally reconstitute a bioactive, postmodern version of the classical GHR binding trough¹.

The crystal structure of dimeric interleukin (IL)-10 bears an extraordinary resemblance to the IFN- γ fold, with just a slightly greater elbow angle of 97° between intercalated helix bundles (ref. 14 and M. R. Walter, personal communication). IL-10R α is squarely in the class 2 cytokine-receptor camp^{1,4,14}, so the structural design of intermediate and signalling IL-10 complexes should closely mirror the IFN- γ case. In contrast, IFN- α/β types are not apparently dimeric in solution, but do associate with the requisite R α and R β subunits to form 1:1:1 heterotrimeric signalling complexes¹⁵ which could best resemble a single IFN- γ or IL-10 helix bundle:R α :R β module and not the prototype 1:2 GH:GHR ensemble¹⁶.

The nucleation of hexameric receptor-cytokine signalling complexes, as is confidently expected for IFN- γ and IL-10 (with concomitant implications for intracellular signalling^{13,15}), has given physical form to an emerging trend in the haematopoietic system. The crystal structures of leukaemia inhibitory factor (LIF)⁵, ciliary neurotrophic factor (CNTF)¹⁷ and a robust model of IL-6 (ref. 18) fold very similarly to GH but display a puzzling three-dimensional patchwork of receptor epitopes that overwhelm the simple, two-site binding model of a stand-alone GHR-like dimer complex. A higher order 'complex of complexes' parsimoniously solves this quandary for IL-6 in a 2:2:2 association with IL-6R α and gp130 (ref. 18) and provides a pleasing model for LIF, CNTF, oncostatin-M, cardiotrophin, IL-11 and IL-12 multimeric signalling complexes^{5,18}.

However, for other helical cytokines that are tied together as solution dimers¹ and might be expected to act as IFN- γ -like aggregators, the evidence is to the contrary. The primary receptor epitope on

IL-5 straddles the interlaced dimer⁴ interface so that the D-helix binding of a first R α subunit is a symmetry-breaking event that sterically occludes the other R α docking site, and forces the choice of a contrary, single R β A-helix site¹⁹. On the other hand, the disulphide-bridged macrophage colony-stimulating factor (MCSF) dimer⁴ does act as a bridge, but only between a pair of identical fms/CSF-1 tyrosine kinase receptors (not superfamily molecules) which each bind a symmetry-related A-helix site per monomer using Ig domains²⁰.

Walter and colleagues' structure¹ of the IFN- γ R α complex* offers a new organizing principle for class 2 cytokine receptors, and a welcome lead to understanding the greater associations of a large segment of the class 1 receptor family. The two cytokine-binding geometries exhibited by the GHR² and the IFN- γ R α ¹ hopefully signal two extremes, but the latitude between them is great — modellers should beware of blindly using one or the other as a template¹⁶. Nonetheless, the basic rules underlying the molecular recognition of IFN- γ or GH by disparate receptors seem to be reassuringly similar. Allusions and cautions aside, it remains gratifying to see how rapidly this field is being propelled by force of its protein structures. On to the next! □

J. Fernando Bazan is in the Department of Molecular Biology, DNAX Research Institute, 901 California Avenue, Palo Alto, California 94304-1104, USA.

1. Walter, M. R. *et al. Nature* **376**, 230–235 (1995).
2. deVos, A. M., Ultsch, M. & Kossiakoff, A. A. *Science* **255**, 306–312 (1992).
3. Bazan, J. F. *Proc. natn. Acad. Sci. U.S.A.* **87**, 6934–6938 (1990).
4. Sprang, S. R. & Bazan, J. F. *Curr. Opin. struct. Biol.* **3**, 815–827 (1993).
5. Mott, H. R. & Campbell, I. D. *Curr. Opin. struct. Biol.* **5**, 114–121 (1995).
6. Harlos, K. *et al. Nature* **370**, 662–666 (1994).
7. Muller, Y. A., Ultsch, M. H., Kelley, R. F. & deVos, A. M. *Biochemistry* **33**, 10864–10870 (1994).
8. Somers, W., Ultsch, M., DeVos, A. M. & Kossiakoff, A. A. *Nature* **372**, 478–481 (1994).
9. Clackson, T. & Wells, J. A. *Science* **267**, 383–386 (1995).
10. Mian, I. S., Bradwell, A. R. & Olson, A. J. J. *J. molec. Biol.* **217**, 133–151 (1991).
11. Flocco, M. M. & Mowbray, S. L. *J. molec. Biol.* **235**, 709–717 (1994).
12. Stanfield, R. L. & Wilson, I. A. *Trends Biotech.* **12**, 275–279 (1994).
13. Marsters, S. A. *et al. Proc. natn. Acad. Sci. U.S.A.* **92**, 5401–5405 (1995).
14. Zdanov, A. *et al. Structure* **3**, 591–601 (1995).
15. Cohen, B., Novick, D., Barak, S. & Rubenstein, M. *Molec. cell. Biol.* (in the press).
16. Seto, M. H. *et al. Protein Sci.* **4**, 655–670 (1995).
17. McDonald, N. Q., Panayotatos, N. & Hendrickson, W. A. *EMBO J.* **14**, 2689–2699 (1995).
18. Paonessa, G. *et al. EMBO J.* **14**, 1942–1951 (1995).
19. Tavernier, J. *et al. Proc. natn. Acad. Sci. U.S.A.* **92**, 5194–5198 (1995).
20. Taylor, E. W., Fear, A. L., Bohm, A., Kim, S.-H. & Kothe, K. *J. biol. Chem.* **269**, 31171–31177 (1994).

*I have learned that a similar X-ray structure has just been solved using MAD phasing by S. Ealick, F. Winkler and co-workers at Cornell University and Hoffman-La Roche (ACA Abstr. W130, Montreal, July 1995).

Silent intervals

We all hate unexpected loud noises. Sudden crashes and explosions can startle us badly, and even damage our ears. Daedalus now has an answer.

His first idea was a sort of powered flap which snapped over the ear canal on command. Being so close to the ear, it made more noise than the sound it was keeping out. He then recalled those electro-rheological fluids, typically suspensions of fine particles in an insulating oil, whose viscosity rises in an electric field. The particles each acquire a dipole, and clump together into a tenacious structure which disperses when the field is turned off. It all happens in milliseconds, and in total silence. Daedalus is now using such fluids in a silent, fast-acting, electrically controlled earplug.

The prototype is a little hollow tube blocked by a succession of diaphragms soaked in a suitable electro-rheological fluid. With the field off, the diaphragms are perfectly flexible and sound travels down the tube as if they weren't there. But when the field is on, they lock up into stiff, highly damped barriers which reflect most of the sound and absorb the rest. The earplug will be wired to a small control box that nestles behind the ear like a miniature hearing aid. This in turn will get its orders by short-range radio.

The primary market will be military. To 'silence' a gun or grenade, a little transmitter will be attached to it, so that it sends out a radio pulse just before it goes off. Next time the special forces storm some luckless gang of terrorists, firing guns and throwing stun grenades, they will do so in blissful, contemplative quiet. Their radio earplugs will neatly clip out the noise of their own explosions, while leaving their ears open for the quiet exchange of orders and the panicky cries of their victims. Meanwhile, the victims will be deafened and disoriented by the stunning racket of the assault.

A simpler, less selective arrangement could exploit the slow speed of sound. A tiny microphone on a stalk a few centimetres away from the ear could detect an approaching bang, and switch on the earplug before the bang reached it. Such pre-emptive earplugs would be widely welcomed by boiler-makers, engineers and the parents of clumsy or hyperactive children. They might best be tuned not to exclude loud pulses, but merely to reduce them to a steady level. Pop music, that universal annoyance, could be tamed in this way. Normalized to one intensity, deprived of all amplitude modulation, it will lose its insistent beat. It will be reduced to a rhythmless drizzle of relatively unobtrusive frequency-modulated noise.

David Jones