PROTEIN STRUCTURE

Folding forecast

Being able to predict the tertiary structure of a protein from its primary sequence is one of the most important goals for protein researchers, but has, so far, been a task beyond capabilities. But a study by Simmerling, Strockbine and Roitberg in *The Journal of the American Chemical Society* shows for the first time how this could now be possible using computer simulations.

The researchers looked at the smallest protein known to show normal folding properties — a 20-residue sequence called 'Trpcage', created by Niels Andersen and colleagues — and carried out a series of molecular dynamics simulations, starting from only the primary sequence of Trpcage. The best structure was chosen purely on the basis of lowest energy, not from any structural features or sequence similarity to known protein structures. This was then sent back to the Andersen group before the NMR structural data were released.

The correlation between the two sets of data was impressive. Structural details, including the arrangement of the hydrophobic core and a short α -helix, were picked up by the simulation. The correspondence between

the chemical-shift deviations was also good, and both methods showed that the charged terminal residues adopted multiple conformations. The computer simulation also uncovered structural details that were not apparent from the NMR data, such as an Asp–Arg bridge, the presence of which is supported by other experiments.

So, it seems that computer simulations could at last be used to predict the three-dimensional structure of a protein accurately. Also, the use of energy as a successful scoring function suggests that we understand the underlying interactions that determine folding. And although there are obvious challenges when applying this to larger, more complex proteins, this could be a very important tool for drug design.

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References and links

ORIGINAL RESEARCH PAPER Simmerling, C., Strockbine, B. & Roitberg, A. E. All-atom structure prediction and folding simulations of a stable protein. *J. Am. Chem. Soc.* **124**, 11258–11259 (2002)

FURTHER READING Neidigh, J. W., Fesinmeyer, R. M. & Andersen, N. H. Designing a 20-residue protein. *Nature Struct. Biol.* **9**, 425–430 (2002)

WEB SITE
Horizon Symposia — protein folding and disease:
<http://www.nature.com/drugdisc/horizon/>

IN BRIEF

ANTICANCER DRUGS

Reaction path of protein farnesyltransferase at atomic resolution.

Long, S. B. *et al. Nature* **419**, 645–650 (2002)

Protein farnesyltransferase (FTase) attaches a lipid group that is necessary for proper function to various signal-transduction proteins, including RAS proteins, which are associated with ~30% of human cancers. Inhibitors of FTase cause tumour regression in animals, and several are now in clinical trials. On the basis of the crystal structures of a series of FTase complexes, Long *et al.* describe the reaction path of the enzyme at atomic resolution, which indicates that known FTase inhibitors act at two different sites and highlights further possibilities for structure-based drug design.

G-PROTEIN-COUPLED RECEPTORS

Functional immobilization of a ligand-activated G-protein-coupled receptor.

Neumann, L. *et al. ChemBioChem* **3**, 993–998 (2002)

Generating arrays of G-protein-coupled receptors (GPCRs) for high-throughput screening is challenging because they typically need to be embedded in membranes to maintain their correctly folded conformations. Neumann *et al.* have developed a simple method to immobilize GPCRs on gold and glass surfaces that allows real-time assessment of the protein conformation, which they demonstrate by monitoring agonist activation of the β_2 -adrenoceptor, a prototypical GPCR.

NANOTECHNOLOGY

Nanocrystal targeting *in vivo*.

Åkerman, M. E. *et al. Proc. Natl Acad. Sci. USA* **99**, 12617–12621 (2002)

Nanoparticles are thought to have potential as novel intravascular probes for both diagnostic and drug delivery purposes (see the article by Langer and colleagues on page 77 of the January issue). A key issue is the ability to target specific tissues and cell types. By attaching peptides that recognize markers known to be expressed at particular vascular sites to quantum dots — nanocrystals that have luminescent properties — the authors show that nanocrystals can be targeted *in vivo* with high specificity.

ANTICANCER DRUGS

A mouse model of human oral-esophageal cancer.

Opitz, O. G. *et al. J. Clin. Invest.* **110**, 761–769 (2002)

Cancers of the oral cavity and the oesophagus are common worldwide and have a poor prognosis, but development of improved therapies has been hampered by the lack of good animal models. Opitz *et al.* now report the generation of the first genetically based animal model of these diseases, which faithfully replicates the human disease and should facilitate the identification of cooperating genetic alterations and the testing of chemopreventive and therapeutic agents.