Rapamycin 'glue strategy'

Rapamycin is a highly specialized molecular glue. That is the essence of a recently published paper [*Science* (1996) 273, 239–242] on the structure of this immunosuppressive agent associated with two of its binding proteins: the FK506-binding protein (FKBP12) and the FKBP-rapamycin-associated protein (FRAP). The structure was determined in the laboratory of Dr Jon Clardy at Cornell University (Ithaca, NY, USA) in collaboration with Dr Stuart Schreiber and coworkers at Harvard University (Boston, MA, USA).

A striking aspect of the complex is the almost complete absence of physical interaction between the two protein molecules. The complex is held together by the simultaneous insertion of two distinct regions of rapamycin into hydrophobic clefts on the surface of FKBP12 and FRAP. The binding occurs sequentially; first, rapamycin and FKBP12 form a complex and then FRAP binds to its complementary region of rapamycin. The role of rapamycin is to serve as a tether, holding two disparate proteins in close proximity.

Cyclosporin is another immunosuppressive agent that acts by forming a ternary complex with two proteins: cyclophylin and calcineurin, a protein serine/threonine phosphatase. Again, the binding is sequential; cyclosporin and cyclophylin interact first, and then a ternary complex is formed with calcineurin, which inhibits its phosphatase activity. In contrast to rapamycin binding, the binding site for calcineurin is spread over the surface of both cyclosporin and cyclophylin.

Both rapamycin and cyclosporin are naturally occurring cyclic peptides that were originally discovered from soil microbes as antifungal agents. They both possess potent immunosuppresive activity, but have distinct mechanisms of action. Cyclosporin inhibits the signaling pathway leading from the T-cell receptor to the activation of the IL-1 gene, presumably through inhibition of the phosphatase activity of calcineurin. Rapamycin blocks the signaling pathway leading from the IL-1 receptor to the nuclear factors that trigger cell proliferation, perhaps through inhibition of FRAP. FRAP is a member of a class of proteins that are known to be important in cell-cycle progression and regulates the p70 ribosomal protein, S6 kinase. Entrapping FRAP in a complex with rapamycin and FKBP12 probably blocks its ability to regulate the p70 kinase.

The work from Clardy's laboratory may also lead to the development of new tools for genetic engineering. By splicing the rapamycin-binding domains from FKBP12 and FRAP onto other proteins, it will be possible to use the rapamycin glue to join proteins that would otherwise never associate. This may have practical value for gene therapy. According to Clardy, "It's not hard to introduce new genes. What's hard is getting them to turn on." Already, scientists from Ariad Pharmaceuticals (Cambridge, MA, USA) have used the rapamycin glue strategy to join a DNA-binding protein with a regulatory protein to trigger a foreign gene in mice to produce human growth hormone. The ability to tether proteins by this mechanism may be an important key to making the promise of genetic therapies a reality.

Robert W. Wallace

Strategic use of drug delivery systems

The pharmaceutical industry is indeed 'living in interesting times', but not with the doom and gloom forecast by that Chinese curse. Behind the recent media attention focusing on multi-million-dollar mergers and acquisitions surrounding the big players, there is much growth and dynamism within the industry, centring around small organizations that focus on niche drug delivery technology. Such technology can provide benefits both commercially to the pharmaceutical company and clinically to the patient. The pharmaceutical industry is changing in attitude and culture towards the needs of the 'customer', and drug delivery systems (DDS) are playing an increasing role in meeting these needs. This was a recurring theme at a two-day IBC conference held in June, entitled *The Strategic Use of Drug Delivery Systems.*

DDS in strategic marketing

Dr Lisa Nolan (Elan Corp, Athlone, Ireland) set the scene for the first day's proceedings by providing a strategic marketing perspective. She highlighted the clinical benefits of DDS, which often translate commercially. Specialized delivery technology can prove lifesaving to important new chemical entities that would otherwise drop out of development owing to inappropriate pharmacokinetics. From a commercial perspective, a novel therapeutic may make it to the market, but if it has a suboptimal dosage regime or delivery system, it is susceptible to market share erosion; this point is particularly important in the current climate in which the period of pioneer exclusivity is decreasing. Life-cycle management of a product through the strategic use of DDS in line extension can prove highly important. This is exemplified by the success story of Cardizem™ (diltiazem) in the US angina market: Marion Merrell Dow used an internal cannibalization strategy to increase the market share of their once-daily formulation after the initial diltiazem formulation patent expiry. The lack of availability of delivery technology in-house may, however, be the stumbling block to product line extension. In that case, the