DRUG DELIVERY

Biodegradable multi-drug dispenser

Have you ever forgotten to take your daily pills at the right time? Or missed one altogether? Although important, forgetfulness is not the only problem with drug delivery. Traditionally, most drugs are delivered by oral or intravenous means, which can lead to high concentrations of drugs in the bloodstream with concomitant toxic side effects, and yet only a small percentage of the drug actually reaches the target area. An ideal drug delivery system would maintain optimum therapeutic concentrations of the drug in the target tissue, with minimum fluctuation and allow reproducible release of the drug for long periods of time. In a study published in the November issue of *Nature Materials*, Langer and colleagues from MIT report a biodegradable drug delivery system with the potential to release pulses of different drugs at various intervals after implantation by using materials of different molecular masses for the membranes covering the drug-containing reservoirs.

The microchip device, made from a degradable polymer, was designed to achieve multi-pulse drug release over periods of several months, without requiring a stimulus to trigger the drug release. Reservoirs machined through a polymer disc were blocked on one side with a layer of degradable polyester tape, loaded with the drug to be released and then sealed with degradable polymeric membranes. Drugs could be released at defined times on the basis of the characteristics of the reservoir membranes. The material used, the molecular mass and the thickness all contribute to the degradation rate of the membrane, and therefore the rate of drug release. The devices were about 11.9 mm in diameter and about 500 μm thick.

Proof-of-principle studies were conducted *in vitro* with microchips made from poly(L-lactic acid) (PLLA) that used poly(lactic-co-glycolic acid) (PLGA) reservoir membranes of various molecular masses to control the release of test chemicals dextran, heparin and human growth hormone. A 50/50 ratio of lactic acid/glycolic acid was chosen for the membrane as this provides a degradation time of a few weeks to months. In addition, a range of PLGA molecular masses — 4,400, 11,000, 28,000 and 64,000 — were chosen. The results showed four

ANTIPYRETIC DRUGS

Heat relief

Inflammatory molecules called prostaglandins (PGs) facilitate induction of the febrile response to infection. Fever-alleviating drugs, such as ibuprofen, are used by millions of people every day, and act by inhibiting cyclooxygenase (COX), which catalyses the first step in the formation of PGs from arachidonic acid. But the use of COX inhibitors is associated with severe side effects, such as gastric intolerance and depression of blood clotting, which are probably related to their non-specific effects on the synthesis of several PGs. Targeting PGs that are specifically involved in eliciting fever might permit the development of antipyretic drugs with an improved safety profile. A study published recently in *Nature Neuroscience* brings us one step closer to realizing this goal.

A team led by Anders Blomqvist investigated the role of microsomal prostaglandin E synthase-1 (mPGES-1) — which catalyses the second step in PGE_2 production — in the febrile response, by knocking out its expression in mice. Mutant mice were indistinguishable from their wild-type littermates under normal physiological conditions. However, differences emerged following immune challenge with bacterial cell-wall lipopolysaccharide (LPS). Shortly after injection of LPS, the core body temperature of wild-type mice increased significantly and remained elevated for about six hours. By contrast, the temperature of immune-challenged mPGES-1-deficient mice did not differ from that of saline-injected controls. Direct injection of PGE_2 into the brains of mutants elicited a robust febrile response, confirming that these mPGES-1-deficient mice retained the capacity to respond to the product of mPGES-1 activity.

Levels of PGE_2 in cerebrospinal fluid after administration of LPS mimicked the temperature pattern, increasing in wild-type subjects and remaining static in their mutant counterparts. Incubation of brain homogenates from immune-challenged mice with PGH_2, the substrate of mPGES-1, showed that these responses were correlated with enzymatic activity, or lack thereof, in the microsomal fraction. Reverse transcription-polymerase chain reaction was used to confirm that the physiological effects of LPS injection were due to differential expression of mPGES-1 in brain homogenates of wild-type and mutant mice.

Interestingly, expression of another PG-synthesizing enzyme — mPGES-2 — was not upregulated by immune challenge in wild-type mice, indicating that mPGES-1 is specifically involved in facilitating fever. Similarly, the response of COX-2 to LPS injection was not affected by the mPGES-1 mutation, being upregulated in both mutant and wild-type mice. These results show that, unlike present-generation COX inhibitors, compounds that target mPGES-1 should specifically inhibit the synthesis of fever-inducing PGE_2, without affecting the production of other PGs. Side effects of antipyretic drugs might thereby become a thing of the past.

Suzanne Farley

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clear pulses of drug over a two-month period as each of the reservoir membranes sequentially degraded and opened. It seems that the driving force for the opening of the membranes comes from water uptake and swelling of the polymer, which is counterbalanced by the mechanical strength of the polymer. Materials with higher molecular masses retain their mechanical strength for longer periods, leading to drug release at later times.

By varying the size and polymer composition of the microchip, the number and volume of the reservoirs, and the composition of the membranes, these devices could offer the opportunity to tailor specific release times of chemicals, as well as enabling the construction of complex release profiles that provide both pulsatile and continuous release of different drugs or chemicals.

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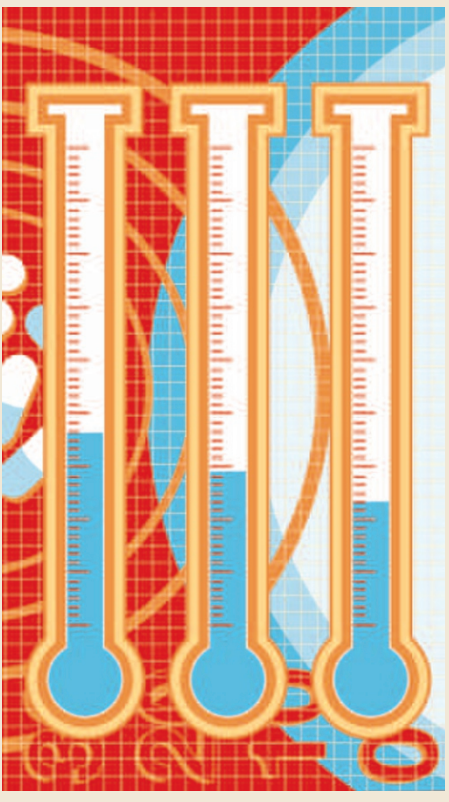

VIRTUAL SCREENING

Different routes to the same answer

High-throughput screening (HTS) of large compound libraries (typically ~10^5–10^6 compounds) is widely established as a key component of the drug discovery programmes of many organizations, but requires considerable resources. Virtual screening (VS) is much less demanding in this respect, but are the chances of identifying 'hits' as good? So far, studies directly comparing the success of the two approaches in hit identification are rare. However, the results of two recent studies — one using HTS and one using VS — which both identified the same inhibitor of the Type I transforming growth factor-β (TGF-β) receptor kinase (TβRI), provide evidence that appropriately guided VS approaches can be as successful as HTS.

The TGF-β signalling pathway seems to have an important role in a range of disease states, including fibrosis and cancer, and TβRI is a key enzyme in this pathway. So, Sawyer *et al.* set out to identify inhibitors of TβRI by HTS of a large compound library in a TGF-β-dependent cell-based assay. Promising hits were then further evaluated for their ability to inhibit a constitutively active form of the TβRI kinase domain, which led to the identification of a potent diheteroaryl-substituted pyrazole compound (IC_{50} = 51 nm) that was chosen for further development. The structural relationship of this hit compound to known inhibitors of p38 mitogen-activated protein (MAP) kinase led the authors to test its effect on this enzyme, and indeed, the compound did show some inhibitory activity (IC_{50} = 740 nM). Structure–activity studies using the hit compound as a starting point produced two series of compounds with members that retained potent TβRI inhibitory activity, and one of these series contained compounds that also showed good (>100-fold) selectivity over p38 MAP kinase, which could be rationalized by using crystallographic data on kinase-domain–inhibitor complexes.

The second study, by Singh *et al.*, used knowledge on a previously characterized p38 MAP kinase inhibitor with relatively weak inhibitory activity against TβRI (30 μm) to design a computational 'query' — based on the position and presence of key structural features, and also compound shape — for virtually screening a commercially available 200,000-compound library. The query gave 87 diverse compounds that satisfied the structural-feature and shape constraints, and when these compounds were tested in an *in vitro* assay evaluating inhibition of TβRI kinase activity, the same diheteroaryl-substituted pyrazole as that found by Sawyer *et al.* was identified. The authors also determined a crystal structure of this inhibitor in complex with the TβRI kinase domain, which confirmed the predicted binding interactions, validating their directed virtual-screening hypothesis.

The study by Singh and colleagues clearly highlights the growing potential of VS as an inexpensive and rapid strategy for hit identification. But, of course, VS and HTS are not mutually exclusive. The next few years are likely to see both being used in an increasingly complementary manner, with the 'best' overall approach to screening in any particular case depending heavily on the strengths of the organization involved and the target being pursued.

Peter Kirkpatrick

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