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.

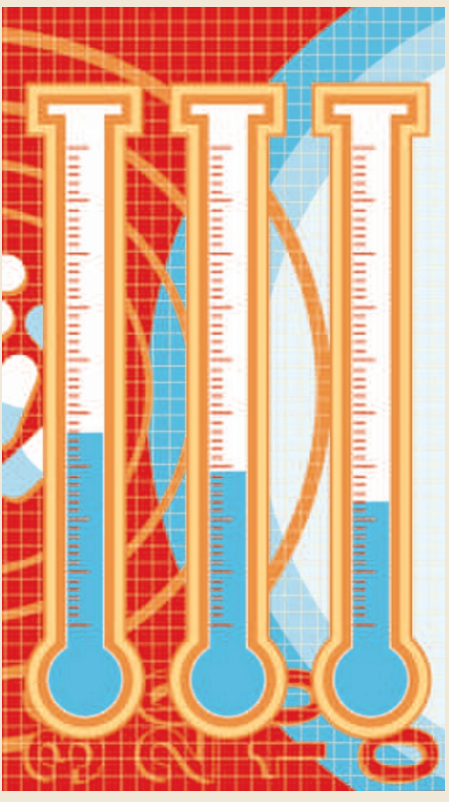
By varying the size and polymer composition of the microchip, the number and volume of the reservoirs, and the composition of the membranes, these devices could offer the opportunity to tailor specific release times of chemicals, as well as enabling the construction of complex release profiles that provide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

*Melanie Brazil*


### References and links

**ORIGINAL RESEARCH PAPER** Richards Grayson, A. C. *et al*. Multi-pulse drug delivery from a resorbable polymeric microchip device. *Nature Materials* **2**, 767–772 (2003)

**FURTHER READING** Duncan, R. The dawning era of polymer therapeutics. *Nature Rev. Drug Discov.* **2**, 347–360 (2003)

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.

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### References and links

**ORIGINAL RESEARCH PAPERS** Sawyer, J. S. *et al.* Synthesis and activity of new aryl- and heteroaryl-substituted pyrazole inhibitors of the transforming growth factor-β type I receptor kinase domain. *J. Med. Chem.* **46**, 3953–3956 (2003) | Singh, J. *et al.* Successful shape-based virtual screening: the discovery of a potent inhibitor of the type I TGFβ receptor kinase (TβRI). *Bioorg. Med. Chem. Lett.* **13**, 4355–4359 (2003)

**FURTHER READING** Bajorath, J. Integration of virtual and high-throughput screening. *Nature Rev. Drug Discov.* **1**, 882–894 (2002)