IN BRIEF

GENE THERAPY

Molecular ablation of ventricular tachycardia after myocardial infarction.

Sasano, T. *et al. Nature Med.* **12**, 1256–1258 (2006)

Individuals who suffer a myocardial infarction are often subsequently at risk of ventricular tachycardia (VT). Recent problems with defibrillator implantation, the only therapeutic option for patients at risk from this complication, has led to the search for alternative treatment strategies. In a proof-of-principle study, Sasano *et al.* demonstrate that transferring a gene encoding a dominant-negative version of the KCNH2 potassium channel to the border of the infarct scar eliminated all ventricular arrhythmias in a porcine model of inducible VT.

DIABETES

Production of pancreatic hormone-expressing endocrine cells from human embryonic cells.

D'Amour, K. A. *et al. Nature Biotechnol.* **24**, 1392–1401 (2006)

Attempts to differentiate human embryonic stem cells into insulin-producing cells for potential therapy of diabetes have been hindered by inefficiency of differentiation and the low insulin content of the resulting cells. Now, in a crucial step forward, D'Amour *et al.* describe a differentiation process in which cells are directed through different stages of development that mimic *in vivo* pancreatic organogenesis. The result is differentiated endocrine cells that are capable of synthesizing the pancreatic hormones insulin, glucagon, somatostatin, pancreatic polypeptide and ghrelin, and have an insulin content similar to that of adult pancreatic islets.

ANTIBACTERIAL DRUGS

A linguistic model for the rational design of antimicrobial peptides.

Loose, C. *et al. Nature* **443**, 867–869 (2006)

The antimicrobial peptides (AmPs) made by many organisms to ward off bacterial infection are thought to be less susceptible to the development of resistance and so represent an attractive new class of antimicrobial drugs. This paper describes the rational design of a set of peptides using a 'linguistic model' of naturally occurring AmPs, which involves viewing the amino-acid sequences of these peptides as a language to which a set of grammars is assigned. This grammar set is then used to create novel, unnatural AmP sequences. The authors identified several peptides with bacteriostatic activity against various bacterial species, including *Staphylococcus aureus* and *Bacillus anthracis*.

CANCER

Targeting β_2-microglobulin for induction of tumor apoptosis in human hematological malignancies.

Yang, J. *et al. Cancer Cell* 295–307 (2006)

Levels of β_2-microglobulin (β_2M), part of the major histocompatibility complex (MHC) class I molecule, are elevated in several haematological malignancies. While studying the importance of this using an anti-β_2M monoclonal antibody (mAb), Yang *et al.* noticed that the mAbs had a strong apoptotic effect on the cancer cells. Here they describe how recruitment of MHC class I molecules to lipid rafts initiates a series of events that culminates in caspase-9-dependent apoptosis. The anti-β_2M mAbs had potent anticancer activity in several haematological tumour cell lines and against established tumours in animal models, and also good toxicity profiles.

LEAD DISCOVERY

Bits and pieces

Fragment-based approaches to lead discovery — in which low-molecular mass, weakly binding 'fragments' are transformed into highly potent larger molecules by various design strategies — have become increasingly popular in recent years. By taking a reverse 'deconstructive' approach and investigating the characteristics of fragments that might be derived from high-affinity lead compounds, two recent papers now provide insights that could be valuable for fragment-based lead discovery.

In the first paper, by Babaoglu and Shoichet in *Nature Chemical Biology*, the authors investigate the question of whether a higher-affinity inhibitor can always be parsed into component fragments that will still bind to the target protein in geometries corresponding to those observed in the original inhibitor.

Contrary to their expectations, when they deconstructed a previously known β-lactamase inhibitor into three fragments, none of them bound in a position that recapitulated its position in the larger molecule. As the authors note, their findings suggest that in some cases, good inhibitors might be missed by fragment-based approaches.

The second paper, from Hadjuk in the *Journal of Medicinal Chemistry*, considers the crucial issue of the impact of fragment potency on the likelihood of transforming an initial fragment into a more potent lead with appropriate drug-like properties. Hadjuk performed a retrospective analysis of 18 highly optimized inhibitors, in which the compounds were systematically deconstructed until the minimum binding elements could be identified. Analysing the potency changes that were observed as the leads were reduced in size revealed a nearly linear relationship between molecular mass and binding affinity over the entire range of sizes and potencies represented in the dataset.

On the basis of these data, Hadjuk suggests that one conclusion that can be drawn is that while following an ideal path from optimized fragment to optimized drug lead, every mass unit that is added to the initial fragment contributes equally and proportionally to the binding affinity. This has several potentially important implications for fragment-based lead discovery, as the author notes. First, the constancy in the binding efficiency (affinity/mass) could be used as a quantitative measure of effective fragment elaboration. Second, the data emphasize the importance of beginning with the most efficient fragment lead, regardless of absolute potency or molecular mass, because if efficiency (or inefficiency) remains constant during optimization, then beginning with an inefficient fragment will make optimization more challenging. Appropriate use of such relationships should increase the chances of success of future fragment-based lead discovery programs.

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ORIGINAL RESEARCH PAPERS Babaoglu, K. & Shoichet, B. K. Deconstructing fragment-based inhibitor discovery. *Nature Chem. Biol.* 29 Oct 2006 (doi: 10.1038/nchembio831) | Hadjuk, P. J. Fragment-based drug design: how big is too big? *J. Med. Chem.* 9 Nov 2006 (doi: 10.1021/jm060511h)
FURTHER READING Rees, D. C. *et al.* Fragment-based lead discovery. *Nature Rev. Drug Discov.* **3**, 660–672 (2004)