IN BRIEF

SEXUAL DYSFUNCTION

Discovery of 2-(4-pyridin-2-ylpiperazin-1-ylmethyl)-1*H*-benzimidazole (ABT-724), a dopaminergic agent with a novel mode of action for the potential treatment of erectile dysfunction.

Cowart, M. *et al. J. Med. Chem.* **47**, 3853–3864 (2004)

Selective facilitation of sexual solicitation in the female rat by a melanocortin receptor agonist.

Pfaus, J. G. *et al. Proc. Natl Acad. Sci. USA* **101**, 10201–10204 (2004)

The considerable success of phosphodiesterase 5 inhibitors, such as sildenafil (Viagra; Pfizer), in the treatment of erectile dysfunction has highlighted the potential of safe and effective pharmacological treatments for sexual disorders. Two possible such agents have been recently reported. Cowart *et al.* discuss the discovery of ABT-724, a selective dopamine D_4 receptor agonist that lacks the side effects typically associated with dopaminergic drugs, and that might represent a new type of drug for erectile dysfunction. Pfaus and colleagues describe the effects of PT-141, a melanocortin receptor agonist that selectively stimulates solicitational behaviour in female rats and that could potentially be used to treat female sexual desire disorders.

CANCER

Twist, a master regulator of morphogenesis, plays an essential role in tumor metastasis.

Yang, J. *et al. Cell* **117**, 927–939 (2004)

Metastasis — a multistep process in which cancer cells disseminate from the site of primary tumours and establish secondary tumours in distant organs — is an important contributor to death in patients with cancer. However, the process is not well understood, hampering efforts for therapeutic intervention. Yang *et al.* show that the transcription factor Twist — which is important in embryonic development — has a key role in tumour metastasis, a discovery that might have both therapeutic and diagnostic applications.

MULTIPLE SCLEROSIS

Oral simvastatin treatment in relapsing-remitting multiple sclerosis.

Vollmer, T. *et al. Lancet* **363**, 1607–1608 (2004)

In addition to their well-known ability to lower cholesterol, some statins have been shown to have immunomodulatory effects that might be beneficial for the treatment of diseases such as multiple sclerosis. Vollmer and colleagues report the results of the first clinical trial of a statin in multiple sclerosis — an open-label study involving 30 patients — which suggested that simvastatin (Zocor; Merck) might inhibit inflammatory components of the disease that lead to neurological disability. This could provide impetus for larger-scale studies to assess the potential use of statins in multiple sclerosis, for which current drugs are only partly effective and expensive.

STATINS

Target audience

Despite their familiarity and undoubted success, statins still retain a veneer of mystery that we are only just beginning to scratch through. One issue, of interest to clinicians and marketing teams alike, is why many patients respond less favourably, or not at all, to statin therapy. Now, a study in the *Journal of the American Medical Association* that examined patients with hypercholesterolaemia that were treated with pravastatin (Pravachol; Bristol-Myers Squibb) is the first systematic study to offer a pharmacogenetic explanation.

In a survey of 148 single nucleotide polymorphisms (SNPs) in 10 genes known to be involved in cholesterol synthesis and statin metabolism — including 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase), squalene synthase, apolipoprotein E and cholesteryl ester transfer protein — Paul Ridker and colleagues found that two polymorphisms in HMG-CoA reductase are associated with reduced efficacy of pravastatin therapy. Individuals heterozygous for SNPs 12 and 29 of the HMG-CoA reductase gene had decreased responses — 22% smaller reduction in total cholesterol and 19% smaller reduction in low-density-lipoprotein cholesterol — compared with individuals who were homozygous for the allele. Looking at the sequence and location of these SNPs, they have no obvious functional effect, so whether they lead to altered HMG-CoA reductase expression or activity, or affect statin binding is uncertain.

As great as the temptation is to translate these results rapidly into a diagnostic test to identify 'non-responders', outstanding questions remain, say the authors. First, do the data extend to other statins? Second, are there dose–response effects? Third, like any other genetic study, can the results be independently confirmed? A further issue is that the proportion of the variance that can be explained by the two HMG-CoA reductase SNPs is small in comparison with the predicted influence of clinical determinants, such as compliance and diet.

But, as Susanne Haga and Wylie Burke state in an accompanying commentary, these findings should force clinicians and policy makers to face two key questions: what evidence justifies the clinical use of a pharmacogenetic test, and what incentives will ensure that the translational research is carried out to provide the evidence? Without attention to these questions, write Haga and Burke, conflicting interests among stakeholders could slow the development of pharmacogenetic approaches to statin therapy or, even worse, lead to changes in practice that are based on speculative or incomplete findings.

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References and links

ORIGINAL PAPER Chasman, D. I. *et al.* Pharmacogenetic study of statin therapy and cholesterol reduction. *JAMA* **291**, 2821–2827 (2004)

FURTHER READING Haga, S. B. & Burke, W. Using pharmacogenetics to improve drug safety and efficacy. *JAMA* **291**, 2869–2871 (2004)