6. Brinkman, R.R., Dubé, M.P., Rouleau, G.A., Orr, A.C. & Samuels, M.E. *Nat. Rev. Genet.* **7**, 249–260 (2006).
7. Lowe, C.E. *et al. Nat. Genet.* **39**, 1074–1082 (2007).
8. Mallareddy, M., Hanes, V. & White, W.B. *Drugs Aging* **24**, 453–466 (2007).
9. Lim, P.O. *et al. Hypertension* **37**, 856–861 (2001).
10. Chopra, P., Randhawa, I. & Chin, T. *Current Drug Ther. (NY)* **7**, 30–35 (2012).
11. Dong, Y.F. *et al. FASEB J.* **25**, 2911–2920 (2011).
12. Gann, P.H., Hennekens, C.H., Ma, J., Longcope, C. & Stampfer, M.J. *J. Natl. Cancer Inst.* **88**, 1118–1126 (1996).
13. van der Lely, A.J. *et al. Lancet* **358**, 1754–1759 (2001).
14. Sekine, K. *et al. Endocrinol. Jpn.* **29**, 653–657 (1982).

Sanseau *et al.* reply:

The response of Wang and Zhang¹ provides further evidence that human genetics data can be used to identify drug repositioning opportunities and highlights the importance of understanding the functional impact of genetic variation to decide whether an antagonist or an agonist is more appropriate (drug directionality). Of course, due diligence must be used in all instances of drug repositioning hypotheses. This new work complements our initial publication, wherein we used genome-wide association studies (GWAS) from the US National Human Genome Research Institute catalog as the source of genetics information², whereas Wang and Zhang started with Online Mendelian Inheritance in Man (OMIM)¹.

Our hypothesis to use GWAS for drug repositioning was supported by evidence that GWAS hits identified phase 3 or marketed drugs^{3,4} and we demonstrated that GWAS findings are enriched for druggable genes². We recognize that in many cases GWAS data do not provide a clear direction as to whether an agonist or an antagonist is needed. Our tables included all hypotheses and were not filtered for direction of effect. As pointed out by Wang and Zhang, the lack of knowledge on directionality could lead to potential side effects rather than therapeutic benefits. This is why it is important to investigate the functional impact of GWAS-associated single-nucleotide polymorphisms. For example, in our paper, we used allelic expression analysis⁵ to establish that the Crohn's disease risk allele was strongly increased expression of the tumor necrosis factor (ligand) superfamily, member 11 gene (*TNFSF11*) in all cell lines and was associated with over expression of *TNFSF11* in CEU B-lymphoblasts and osteoblasts. This suggested that an antagonist could potentially be effective at treating Crohn's disease. Recently, a combination of exome

sequencing combined with a cellular assay demonstrated that loss of function of the melatonin receptor 1B gene (*MTNR1B*) was implicated in type 2 diabetes⁶ suggesting that an *MTNR1B* agonist may be helpful in the treatment of hyperglycemia and type 2 diabetes. *MTNR1B* was initially associated with type 2 diabetes by GWAS⁷ but it was not possible without further evidence to decide if an antagonist or agonist was more appropriate. It is also likely that the recently published ENCODE⁸ data can provide further functional information on the drug directionality.

Using OMIM instead of the GWAS catalog provides a data source with more information on drug directionality and a large number of heritable diseases with a genetic mutation where loss-of-function or gain-of-function information is available. However, equal measures of caution must be employed when using OMIM as a source of repositioning opportunities. It is in fact often not easy to identify gain of function from loss of function from many OMIM entries (similar to the issue of GWAS directionality). Moreover, a recent analysis of the 1000 Genomes data demonstrated that seemingly healthy people had accumulations of mutations reportedly associated with disease in OMIM⁹. This suggests that further validation of OMIM evidence may be required to understand if the identified mutations are truly functional. Although GWAS data are lacking functional information, we still view GWAS as a valuable source of information for identification of potential drug targets in humans, thereby circumventing the risk of failed translation that has dogged the traditional path of

drug discovery through *in vivo* and *in vitro* models. We see the work of Wang and Zhang as highly complementary to ours and welcome continued discussion on applicability and opportunities of using genetic data to identify drug repositioning opportunities for patients in need.

COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details are available in the online version of the paper (doi:10.1038/nbt.2769).

Philippe Sanseau¹, Pankaj Agarwal¹, Michael R Barnes², Tomi Pastinen³, J Brent Richards⁴, Lon R Cardon⁵ & Vincent Mosser⁶

¹Computational Biology Department, Quantitative Sciences, GlaxoSmithKline, Stevenage, UK. ²William Harvey Research Institute, Queen Mary University of London, Charterhouse Square, London, UK. ³Department of Human and Medical Genetics, McGill University and Genome Quebec Innovation Centre, Montreal, Canada. ⁴Departments of Medicine, Human Genetics, Epidemiology and Biostatistics, Lady Davis Institute, Jewish General Hospital, McGill University, Montreal, Canada. ⁵Genetics Department, Quantitative Sciences, GlaxoSmithKline, King of Prussia, Pennsylvania, USA. ⁶Department of Pathology and Laboratory Medicine, CHUV University Hospital, Lausanne, Switzerland. e-mail: philippe.x.sanseau@gsk.com

1. Wang, Z.-Y. & Zhang, H.-Y. *Nat. Biotechnol.* **31**, 1080–1082 (2013).
2. Sanseau, P. *et al. Nat. Biotechnol.* **30**, 317–320 (2012).
3. Collins, F.S. *Sci. Transl. Med.* **3**, 90cm17 (2011).
4. Richards, J.B. *et al. Nat. Rev. Genet.* **13**, 576–588 (2012).
5. Ge, B. *et al. Nat. Genet.* **41**, 1216–1222 (2009).
6. Bonnefond, A. *et al. Nat. Genet.* **44**, 297–301 (2012).
7. Bouatia-Naji, N. *et al. Nat. Genet.* **41**, 89–94 (2009).
8. The ENCODE Project Consortium. *Nature* **489**, 57–74 (2012).
9. Xue, Y. *et al. Am. J. Hum. Genet.* **91**, 1022–1032 (2012).

Vaccine delivery with microneedle skin patches in nonhuman primates

To the Editor:

Transcutaneous drug delivery from planar skin patches is effective for small-molecule drugs and skin-permeable vaccine adjuvants¹. However, to achieve efficient delivery of vaccines and other macromolecular therapeutics into the skin, penetration of the stratum corneum is needed. Topically applied skin patches with micron-scale projections ('microneedles') pierce the upper layers of

the skin and enable vaccines that are coated on or encapsulated within the microneedles to be dispersed into the skin². Although millimeter-scale syringes have shown promise for vaccine delivery in humans³ and technologies, such as the Dermalroller (Dermalroller, Wolfenbüttel, Germany), exist for creating microscale punctures in the skin for delivery of solutions of therapeutics², solid microprojection microneedles coated with dry vaccine