Rational drug repositioning by medical genetics

To the Editor:
Drug repositioning has been regarded as one of the most promising strategies for translational medicine. Common efforts to find new uses for existing drugs depend on text mining, chemical genetics and network analysis. In the April 2012 issue, Sanseau et al. proposed the use of genome-wide association studies (GWAS) for drug repositioning. This strategy is consistent with the concept that human disease genes are highly druggable and that indications of derived drugs frequently match genetic disease traits. Genetic diseases may result from loss of function (LOF) or gain of function (GOF) of mutated genes, and ligands may behave as agonists or antagonists of targets. If a disease corresponds to a genetic disorder that arises from the GOF (or LOF) of mutated genes, antagonists (or agonists) for the target genes will be potential drugs, whereas agonists (or antagonists) will exert undesirable effects. Therefore, medical genetics–based drug repositioning can be enhanced with information regarding the pathogenesis of genetic diseases and the action mode of ligands.

The catalog of published GWAS data from the US National Human Genome Research Institute does not provide detailed pathophysiological information on genetic diseases; thus, the new uses of old drugs predicted by the GWAS may be side effects. For instance, it was suggested that basiliximab (Simulect) and daclizumab (Zenapax), which target interleukin-2 receptor alpha (IL2RA), might be applied for the treatment of type 1 diabetes. However, as recorded in Drugs.com, diabetes is the clinically identified side effect of the two drugs. The underlying reason is that LOF variation in IL2RA results in diabetes, whereas agonists (or antagonists) will exert desirable effects. Therefore, medical genetics–based drug repositioning can be enhanced with information regarding the pathogenesis of genetic diseases and the action mode of ligands.

We collected 269 successful human drug targets, which are modulated by 983 unique approved drugs, by retrieving the Therapeutic Target Database (TTD; Fig. 1). By comparing successful drug targets with 2,797 human disease genes recorded in OMIM (as of May 24th, 2012), we found that 131 (48.7%) successful targets were associated with inherited diseases (Fig. 1). The indications of drugs that target these genes were then manually compared with genetic disease traits. A total of 135 matches and 535 mismatches between drug indications and genetic disease traits were identified (Supplementary Tables 1 and 2). Examination of the matching drugs and disease traits revealed that all of the drugs are antagonists (or agonists) for targets with GOF (or LOF) features. The 135 matches notably included the most illustrative examples of identical matches derived from GWAS, such as that 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) can lower blood cholesterol levels (hypercholesterolemia). These matches validate the rationality principle mentioned above and strongly suggest that we can apply the principle to find new uses for old drugs and predict drug side effects based on mismatch information. For instance, drosperone, a mineralocorticoid receptor (NR3C2) antagonist, has been approved as an oral contraceptive, whereas NR3C2 agonist fludrocortisone (Florinef) has been indicated for cerebral salt-wasting syndrome. Considering that the GOF alleles of NR3C2 are associated with hypertension, we infer that NR3C2 antagonists have anti-hypertensive effects, whereas NR3C2 agonists have hypertension-inducing side effects.

Indeed, the anti-hypertensive potential of drosperone and the hypertension-inducing property of fludrocortisone with salt have been observed experimentally (Table 1). The preliminary success of this methodology encouraged us to predict new indications and side effects for more drugs. Some illustrative examples that have been experimentally validated are listed in Table 1.

Etanercept is an inhibitor of tumor necrosis factor (TNF). Considering that the GOF alleles of TNF are associated with asthma, TNF inhibition is inferred to have therapeutic effects on asthma. Indeed, the anti-asthma activity of etanercept (Enbrel) has been observed in experiments. Likewise, perindopril (Aceon), an angiotensin-converting enzyme (ACE) inhibitor, can be repositioned to treat Alzheimer’s disease, because the disease may be caused by GOF mutations within ACE. This new indication of perindopril has been revealed in animal models.

Testosterone is a steroid hormone that functions as an agonist that targets the androgen receptor for male hypogonadism. The associated genetic diseases caused by GOF variants of androgen receptor involve prostate cancer. Thus, we infer that testosterone, as an androgen receptor agonist, cannot be repositioned for prostate cancer treatment but has prostate cancer–inducing side effects. Indeed, prostate cancer has been reported as a contraindication of testosterone replacement in men.

Pegvisomant (Somavert), a growth hormone receptor (GHR) antagonist, is an effective medical treatment for acromegaly. Despite the association of GHR mutation with hypercholesterolemia, however, the LOF feature of the mutation implies that hypercholesterolemia is not a new indication of pegvisomant but, rather, its side effect. This side effect of pegvisomant has been previously observed.\(^{13}\) Furosemide targeting solute carrier family 12 member 1 (SLC12A1) is indicated primarily for the treatment of edema associated with congestive heart failure. Because the associated genetic diseases caused by LOF variants of SLC12A1 include Bartter syndrome type I, we infer that furosemide has the risk of inducing Bartter syndrome, which is indeed involved in the side effects of this SLC12A1 inhibitor.\(^{14}\) Using the rationality principle, one can predict new indications and side effects for other drugs from the mismatch information (Supplementary Table 2).

In summary, given the common features of genetic disease genes and drug targets, such as their close links with phenotypes, genes of inheritable diseases are relatively more druggable.\(^{5,6}\) Therefore, if a clinically validated target is connected to a genetic disorder that is beyond its original clinical effect, new uses for the drugs that correspond to this target may be found. However, rational drug repurposing by medical genetics requires analysis of the information combining the pathogenesis of genetic diseases and drug actions. This new concept brings a complementary approach to that previously suggested by Sanseau et al.\(^{4}\) Nevertheless, for a successful drug repurposing project, the results from these methods have to be carefully evaluated by clinical researchers and combined with all available literature and experimental information.

Table 1  Selected examples of predicted new indications and side effects for existing drugs that have been experimentally validated

<table>
<thead>
<tr>
<th>Drug (action)(^{a})</th>
<th>Target</th>
<th>Genetic disease (pathogenesis)(^{b})</th>
<th>Current drug indication(^{c})</th>
<th>New indication or side effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drosiprenone (antagonist)</td>
<td>NR3C2</td>
<td>Hypertension (GOF); pseudohydroaldosteronism type I (LOF)</td>
<td>Oral contraceptive</td>
<td>Hypertension (new indication)</td>
<td>8</td>
</tr>
<tr>
<td>Etanercept (inhibitor)</td>
<td>TNF</td>
<td>Asthma (GOF); vascular dementia (GOF)</td>
<td>Rhenematoid arthritis</td>
<td>Asthma (new indication)</td>
<td>10</td>
</tr>
<tr>
<td>Perindopril (inhibitor)</td>
<td>ACE</td>
<td>Alzheimer’s disease (GOF); myocardial infarction (GOF); renal tubular dysgenesis (LOF)</td>
<td>Hypertension</td>
<td>Alzheimer’s disease (new indication)</td>
<td>11</td>
</tr>
<tr>
<td>Fludrocortisone (agonist)</td>
<td>NR3C2</td>
<td>Hypertension (GOF); pseudohydroaldosteronism type I (LOF)</td>
<td>Cerebral salt-wasting syndrome</td>
<td>Hypertension (side effect)</td>
<td>9</td>
</tr>
<tr>
<td>Testosterone (agonist)</td>
<td>AR</td>
<td>Prostate cancer (GOF); androgen insensitivity (LOF)</td>
<td>Male hypogonadism</td>
<td>Prostate cancer (side effect)</td>
<td>12</td>
</tr>
<tr>
<td>Pegvisomant (agonist)</td>
<td>GHR</td>
<td>Hypercholesterolemia (LOF); short stature (LOF)</td>
<td>Acremegal</td>
<td>Hypercholesterolemia (side effect)</td>
<td>13</td>
</tr>
<tr>
<td>Furosemide (inhibitor)</td>
<td>SLC12A1</td>
<td>Bartter syndrome type I (LOF)</td>
<td>Edema associated with congestive heart failure</td>
<td>Bartter syndrome (side effect)</td>
<td>14</td>
</tr>
</tbody>
</table>

\(^{a}\)Drug actions were obtained by integrating TTD, DrugBank, KEGG Drug and PharmGKB. \(^{b}\)Pathogeneses for genetic diseases were retrieved from OMIM. GOF, gain of function; LOF, loss of function. \(^{c}\)Drug indications for each drug were obtained through a combination of TTD, DrugBank and Drugs.com.
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 Dermaroller (Dermaroller, Wolfenbüttel, Germany), exist for creating microscale punctures in the skin for delivery of solutions of therapeutics4, solid microprojection microneedles coated with dry vaccine