The approach used by Ding *et al.*[1] to identify the main sources of SCF in the haematopoietic niche, although labour-intensive, sets a standard of rigour for researchers studying the bone marrow, and should also be applied to other signals that affect HSCs. Analysis of the gene-expression signatures of specific cells that express other major signalling molecules involved in HSC regulation may allow the identification of marker genes in addition to *Lepr*. These marker genes could be used to isolate cells that support HSC growth from the mesenchymal milieu of the bone marrow. Understanding the complex HSC niche will one day make it possible to create a synthetic microenvironment capable of sustaining long-term HSC growth. ■

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1. Ding, L., Saunders, T. L., Enikolopov, G. & Morrison, S. J. *Nature* **481,** 457–462 (2012).
2. Yamazaki, S. *et al. Cell* **147,** 1146–1158 (2011).
3. Méndez-Ferrer, S. *et al. Nature* **466,** 829–834 (2010).
4. McCarthy, K. F., Ledney, G. D. & Mitchell, R. *Cell Tissue Kinet.* **10,** 121–126 (1977).
5. Aye, M. T. *et al. Exp. Hematol.* **20,** 523–527 (1992).
6. Bilbe, G., Roberts, E., Birch, M. & Evans, D. B. *Bone* **19,** 437–445 (1996).
7. Mercier, F. E., Ragu, C. & Scadden, D. T. *Nature Rev. Immunol.* **12,** 49–60 (2012).
8. Omatsu, Y. *et al. Immunity* **33,** 387–399 (2010).
9. Orkin, S. H. & Zon, L. I. *Cell* **132,** 631–644 (2008).
10. Weisel, K. C., Gao, Y., Shieh, J. H. & Moore, M. A. *Exp. Hematol.* **34,** 1505–1516 (2006).

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DRUG DISCOVERY

Chemical beauty contest

Most drug candidates fail clinical trials, in many cases because the compounds have less than optimal physico–chemical properties. A new method for assessing the 'drug–likeness' of compounds might help to remedy the situation.

PAUL LEESON

Experienced medicinal chemists develop a sense of chemical aesthetics — a feel for how drug-like any particular molecule is. But is it possible to measure such chemical beauty? Reporting this week in *Nature Chemistry*, Hopkins and colleagues[1] provide a quantitative estimate of drug-likeness that assesses a combination of a molecule's physical properties. Unlike the commonly used descriptions of drug-likeness, their approach allows a single, continuous scale to be defined, so that molecules can be ranked in order of desirability.

Drugs are developed from the optimization of 'lead' molecules, which are frequently found through the biological screening of compound collections. Before being finally accepted into use by regulatory and paying bodies, an optimized drug candidate must undergo years of intensive toxicological and clinical-efficacy studies. Most orally active drugs that survive these arduous developmental pressures have a set of physico-chemical properties that fall within a certain range of values — they are said to lie in a defined physical and chemical 'drug-like space'[2–5]. Until now, this drug-like space has been defined using cut-off values for permissible physical properties, perhaps most notably the values defined by the medicinal chemist Christopher Lipinski and his colleagues in the 'rule of five'[2] (Box 1).

Hopkins and co-workers[1] point out that Lipinski's rule can be misleading, because undesirable compounds could pass the drug-likeness test by only just meeting all four cut-off criteria, whereas better compounds could fail because they just miss one of the cut-offs. The application of the rule in this unintended way may help to explain why the compounds in current patents from pharmaceutical companies are, on average, significantly less drug-like than marketed drugs[6–8].

Taking a cue from a study[9] that used mathematical 'desirability functions' to assess how suitable a range of compounds would be as drugs that act in the central nervous system, Hopkins and co-workers[1] used a similar approach to analyse the drug-likeness of a set of 771 oral drugs approved by the US Food and Drug Administration. The authors defined desirability functions for eight physical properties proposed to be important for oral drugs, including the four Lipinksi properties. They also took into account the number of aromatic rings and rotatable bonds in a molecule, the polar surface area (a measure of how hydrophilic a molecule is) and the number of groups in the molecule known to cause toxicity. The functions captured the full distribution of each physical property and provided a continuous quantitative estimate of drug-likeness (QED) on a scale from most to least drug-like.

Because the bulk physical properties of compounds are known to correlate with each other

50 Years Ago

It is the purpose of this article to show that a group of compounds related to lysergic acid diethylamide (LSD-25) produces surfacing behaviour of carp with the movement directed towards the surface … It has been shown previously from work in this laboratory that very small quantities of derivatives of lysergic acid, like lysergic acid diethylamide (LSD-25) and lysergic acid ethylamide (LAE-32), have a surfacing effect on small Siamese fighting fish … After the fish had been exposed to LSD-25 for 10 min., they showed signs of LSD-25 activity. After 30 min. all three fish in the tank containing LSD-25 were at the surface of the liquid in a nose up–tail down position … For the next hour the fish in the tank containing LSD-25 remained at the surface, from time to time moving and even swimming backwards … The fish were returned to the running-water pool after 1.5 hr. In the pool they continued to stay at the surface, moving about but not going to the bottom at all. 2 hr. later they were still at the surface … Experiments in larger tanks, and field trials, are planned.
From *Nature* 27 January 1962

100 Years Ago

I have repeatedly observed the brilliancy of cats' eyes in the dark in particularly favourable circumstances. I have a brilliant incandescent light in my hall, and several cats on the premises. The entrance drive is in a line with the door and the hall lamp. When I call a cat in the chances are that if there she simply sits and looks at me, presenting the spectacle of two small incandescent lights glowing out of the darkness. Light, observer, and cat are all three in line, as observed by Colonel Herschel.
From *Nature* 25 January 1912

to some extent, Hopkins and colleagues used different property weightings to maximize the overall information content of the combined QED values for each drug. This weighting system will be controversial to some, because it may not reflect the importance of each property to drug-likeness. For example, there is a strong case to be made for lipophilicity as the dominant drug-like property, because it is important for a molecule's absorption, metabolism, promiscuity (binding to unwanted targets), toxicity and survival in the drug-development pipeline[3,4,6,7]. Nevertheless, the benefits of the authors' strategy are clear: their method not only computes drug-likeness on a single quantitative scale, but, more importantly, it reveals that drugs that fail the Lipinski criteria have distributions of drug-likeness that overlap with drugs that pass the criteria (Fig. 1).

Hopkins and colleagues went on to show that their QED approach is better at differentiating drugs from non-drugs than the Lipinksi rule and other schemes based on cut-off values. They further validated the discriminatory power of their method by comparing QED scoring with the results of a study[1] in which 79 medicinal chemists decided which of 17,117 molecules were attractive starting points for optimization as drugs, on the basis of only visual inspection of the molecular structures. Impressively, the QED scores for molecules considered to be attractive by the chemists were significantly higher than those for molecules considered unattractive. This suggests that the QED method may, at least in part, capture a sense of the chemical aesthetics that medicinal chemists develop through knowledge, experience and intuition[10].

Finally, Hopkins and co-workers used their method to predict the drug-likeness of 167,045 ligand compounds that bind to 1,729 proteins (on the basis of binding information from ChEMBL, a database of biologically active compounds[11]). This allowed them to determine which proteins had the most drug-like set of ligands. Proteins whose ligands had the highest QED scores should be the most chemically tractable targets for drug discovery, because their known ligands are the most drug-like.

QED is not the final word in understanding the underlying features of chemical beauty and drug-likeness, but it does provide a holistic, more balanced assessment than previous approaches. It is also customizable, highly flexible and seems to be straightforward to implement. Any combination of physical properties can be chosen to define desirability functions, and users can set the relative weightings for properties as desired. QED should therefore find immediate use in replacing cut-off rules for the selection of oral-drug-like compounds for screening. The method can also be applied to control sets other than oral drugs, such as lead-like molecules[12], compounds that belong to specific target and therapeutic classes, and drugs that are administered non-orally.

The widest long-term impact of Hopkins and colleagues' method[1] should be on the optimization of lead compounds, where it will help medicinal chemists to prioritize which drug-like compounds to prepare. It is to be hoped that the implementation of improved guidelines for drug-likeness, such as QED, at this stage of drug discovery will improve the quality[7] of candidate drug molecules, and eventually help to reduce the 96% attrition rate of compounds that enter clinical trials[13]. ■

BOX 1

The Lipinski rule of five

The medicinal chemist Christopher Lipinski and his colleagues analysed[2] the physico-chemical properties of more than 2,000 drugs and candidate drugs in clinical trials, and concluded that a compound is more likely to be membrane permeable and easily absorbed by the body if it matches the following criteria:

- Its molecular weight is less than 500.
- The compound's lipophilicity, expressed as a quantity known as log*P* (the logarithm of the partition coefficient between water and 1-octanol), is less than 5.
- The number of groups in the molecule that can donate hydrogen atoms to hydrogen bonds (usually the sum of hydroxyl and amine groups in a drug molecule) is less than 5.
- The number of groups that can accept hydrogen atoms to form hydrogen bonds (estimated by the sum of oxygen and nitrogen atoms) is less than 10.

The rules, based on the 90-percentile values of the drugs' property distributions, apply only to absorption by passive diffusion of compounds through cell membranes; compounds that are actively transported through cell membranes by transporter proteins are exceptions to the rule. Due in no small part to their simplicity, the Lipinski criteria are widely used by medicinal chemists to predict not only the absorption of compounds, as Lipinski originally intended, but also overall drug-likeness.

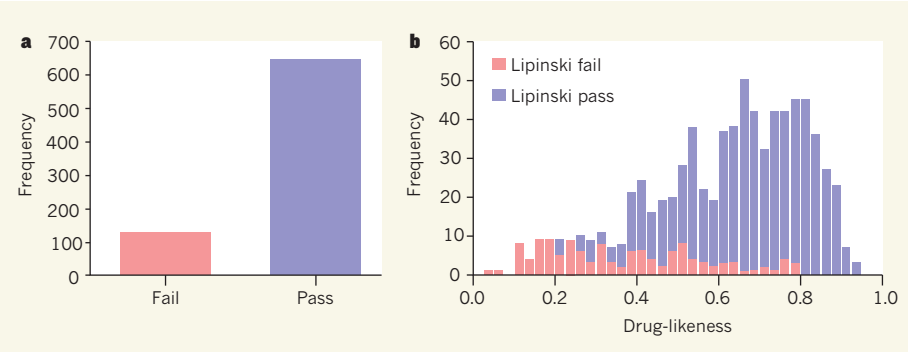

Figure 1 | Assessments of 'drug-likeness'. Physico-chemical criteria, such as those defined by the Lipinski rule of five, are typically used to predict whether a compound is drug-like or not. **a**, The bar chart shows the number of oral drugs that fail or pass the Lipinski rule, based on a set of 771 drugs approved by the US Food and Drug Administration. **b**, Hopkins and colleagues[1] report a method for predicting the drug-likeness of compounds on a scale of 0 (not drug-like) to 1 (drug-like). The chart shows the distribution of drug-likeness calculated using this method for the same drugs depicted in **a**. The analysis shows an overlap of Lipinski passes and failures for a range of drug-likenesses. Notably, some very drug-like molecules fail the Lipinski rule, whereas some very un-drug-like compounds pass it.

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1. Bickerton, G. R., Paolini, G. V., Besnard, J., Muresan, S. & Hopkins, A. L. *Nature Chem.* **4,** 90–98 (2012).
2. Lipinski, C. A., Lombardo, F., Dominy, B. W. & Feeney, P. J. *Adv. Drug Delivery Rev.* **23,** 3–25 (1997).
3. Wenlock, M. C., Austin, R. P., Barton, P., Davis, A. M. & Leeson, P. D. *J. Med. Chem.* **46,** 1250–1256 (2003).
4. Hughes, J. D. *et al. Bioorg. Med. Chem. Lett.* **18,** 4872–4875 (2008).
5. Luker, T. *et al. Bioorg. Med. Chem. Lett.* **21,** 5673–5679 (2011).
6. Leeson, P. D. & Springthorpe, B. *Nature Rev. Drug Discov.* **6,** 881–890 (2007).
7. Leeson. P. D. & St-Gallay, S. A. *Nature Rev. Drug Discov.* **10,** 749–765 (2011).
8. Hann, M. M. *Med. Chem. Commun.* **2,** 349–355 (2011).
9. Wager, T. T. *et al. ACS Chem. Neurosci.* **1,** 435–449 (2010).
10. Lajiness, M. S., Maggiora, G. M. & Shanmugasundaram, V. *J. Med. Chem.* **47,** 4891–4896 (2004).
11. www.ebi.ac.uk/chembldb
12. Teague, S. J., Davis, A. M., Leeson, P. D. & Oprea, T. *Angew. Chem. Int. Edn* **38,** 3743–3748 (1999).
13. Bunnage, M. E. *Nature Chem. Biol.* **7,** 335–339 (2011).