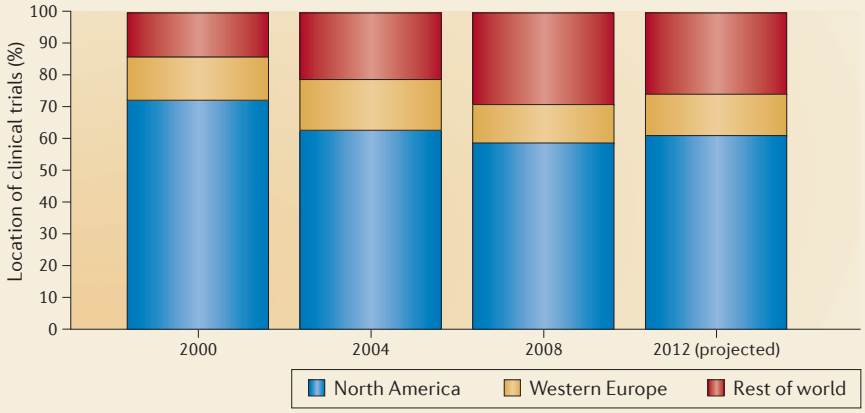
NEWS IN BRIEF

Globalization of clinical trials plateaus?

The off-shoring of clinical trials outside the United States and Europe may have hit a plateau. **The lowdown:** Over the past decade, drug sponsors have increasingly shifted clinical trial programmes from the United States and Europe to the rest of the world. But the Tufts Center for the Study of Drug Development *Outlook 2012* forecasts that trial off-shoring is due to hit a steady state (see figure) because of the complexity and costs of international drug development programmes. "To better manage the costs associated with global development, [drug developers] increasingly are seeking fewer but better performing sites," write the authors. High-profile differences between data derived from different regions — such as apparent variations in the efficacy of AstraZeneca's antiplatelet agent ticagrelor in North America versus the rest of the world in Phase III trials — might also provide a rationale for running trials that will more closely reflect the populations in the main markets in which regulatory approval will be sought.



Source: Tufts Center for the Study of Drug Development.

The NCATS that got the cream

The NIH has received a green light and funding for NCATS, a new centre that will focus on advancing translational science. **The lowdown:** Disappointed with the slow pace with which advances in basic research are translated into new drugs, Francis Collins, Director of the US National Institutes of Health (NIH), said in December 2010 that he wanted to create a National Center for Advancing Translational Sciences (NCATS). One year on, with the signing of the 2012 omnibus spending bill, the NCATS has been approved and funded. The new centre will have a budget of US$575 million for 2012, although most of this reflects a reallocation of funding and programmes that were previously managed by other NIH centres. The new Cures Acceleration Network (CAN), which was authorized in the 2010 health reform law and is intended specifically to accelerate the development of high-need cures, received only $10 million in funding, one-tenth of what the NIH had requested. The NIH is also dissolving the National Center for Research Resources (NCRR).

The NCATS has been controversial since it was first proposed. Some researchers in both the NIH and in industry have argued that the creation of the centre has been rushed and that the money could be better spent on basic research instead of applied research. NIH officials, however, have maintained that the NCATS's focus will leverage academic expertise to complement pharmaceutical and biotech needs. "We need a place to actually look at the whole process of translation in a way that can consider how it might be reengineered, consider how we can make a difference by partnering with both advocacy groups and with industry," Tom Insel, Acting Director of the new centre, told ScienceInsider. The NIH is seeking a director for the centre.

Introducing lead-oriented synthesis

Literature and chemical database analyses suggest that current synthetic approaches tend to produce molecules with poor drug-like properties, so researchers call for the development of 'lead-oriented synthesis' methodologies. **The lowdown:** New 'lead-oriented synthesis' (LOS) methodologies are needed to more effectively populate the viable chemical space for lead compounds, argue Alan Nadin and his colleagues at GlaxoSmithKline in a recent article in *Angewandte Chemie International Edition*. Drug-likeness guidelines, such as Lipinski's rule of 5 (Ro5), note that oral drugs typically have physicochemical properties that fall within defined ranges (such as molecular mass less than 500 Da and LogP less than 5 for Ro5 compliance), but the authors write that few screening hits and leads have properties that are likely to stay within these ranges once candidate optimization begins.

Nadin *et al.* first propose that the ideal lead space should consist of molecules with properties — including a molecular mass of between 200 Da and 350 Da, and a LogP between –1 and 3 — that provide greater flexibility for optimization. When they analysed the 'lead-likeness' of nearly 5 million commercially available screening compounds, however, they found that only 2.6% passed simple filters. Literature analyses similarly found that few newly reported synthesized molecules (2–7%) seem lead-like.

Based on these analyses, they write that current synthetic methodology seems "unintentionally predisposed to producing molecules with poorer drug-like properties". They go on to propose a focus on developing new methodologies for LOS — in particular, robust reactions that work on a range of chemotypes and are tolerant of polar functionalities. "In contrast to target-oriented synthesis, which targets just one compound; diversity-oriented synthesis, which targets scaffold diversity mainly in drug-like space; and combinatorial chemistry, which targets large numbers of compounds, lead-oriented synthesis must be able to deliver molecules with specific molecular properties with utility in the drug discovery and optimization process."

"The challenge now is to make the concept of LOS sustainable and impactful: many readers may be sceptical of the introduction of yet another concept to organic chemistry that describes a seemingly familiar phenomenon. We believe, however, there will be a step change increase in the utility and application of new methodologies which embrace the concepts of LOS," they add.