Quantitative imaging certainly holds tremendous potential for the evaluation of the 'structure-' and 'disease-' modifying capability of drugs versus purely symptomatic relief. However, like Odysseus, we should resist the sound of the sirens. Rather than being seduced by shiny images and/or technically appealing algorithms, we ought to maintain a critical view, and to neither trust images or algorithms, until proven otherwise.

References

1 Pathak, S.D. *et al* (2003) Quantitative image analysis: software systems in drug development trials. *Drug Discov. Today* 8, 451–464
2 Peterfy, C.G. (2000) Scratching the surface: articular cartilage disorders in the knee. *Magn. Reson. Imaging Clin. N. Am.* 8, 409–430
3 Glüer C.C. *et al* (1995) Accurate assessment of precision errors: how to measure the reproducibility of bone densitometry techniques. *Osteoporos. Int.* 5, 262–270
4 Eckstein F. *et al* (2002) Long-term and resegmentation precision of quantitative cartilage MR imaging (qMRI). *Osteoarthritis Cartilage* 10, 922–928
5 Burgkart R. *et al* (2001) Magnetic resonance imaging-based assessment of cartilage loss in severe osteoarthritis: accuracy, precision, and diagnostic value. *Arthritis Rheum.* 44, 2072–2077
6 Graichen, H. *et al*. Quantitative assessment of cartilage status in osteoarthritis with qMRI – technical validation in total knee arthroplasty beyond cartilage volume. *Arthritis Rheum*. (In Press)

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Ultra high quality uHTS

The application of fluorescence detection to HTS and its recent successor, ultra-HTS (uHTS), is well established. This is clear from the wealth of techniques and commercial systems that are discussed in the excellent overview by Stefan Jäger and co-workers that was published recently in *Drug Discovery Today* [1].

In the early days of HTS – the mid-1990s – clients were often presented with a single commercial solution to meet a particular need. The reliability of the chosen instrument was questionable and years of development were needed before satisfactory results could be guaranteed. Together, suppliers and consumers in the field have progressed a long way; diverse and skilled teams of engineers and scientists have worked synergistically to bring much improved instruments to the market.

Eggeling *et al.* also describe the many established and novel fluorescence methods that have been adapted to the demanding conditions of uHTS [1]. Among these, microscopic fluorescence shows great promise in the delivery of not only ultra high throughput but also ultra high quality. Despite similar advances in liquid handling in the low microliter and nanoliter range [2], experimental error in reagent dispensing is the main cause of false positives in screening campaigns. Miniaturization enables replication of experiments to minimize the impact of errors without increasing spending on reagents. Furthermore, microscopic fluorescence provides an insight into the binding events and reagent concentrations in every well, enabling the correction of errors in liquid handling or sample processing (e.g. mixing or evaporation).

Although the new fluorescent techniques are promising, uHTS will never become the universal solution for drug discovery, as recently pointed out by Schmid [3]. However, following years of capital investment, automated compound testing can be seen as an efficient engine to facilitate drug discovery if, and only if, it is fueled with the right targets and compounds.

Discovery scientists are still trying to answer the fundamental question: where are the drugs that genomics and HTS promised to deliver? The average time frame for the development of a drug is estimated to be 15 years. HTS started to be applied in the early 1990s, only being seriously refined and implemented in the late 1990s (for example, Lipinski's landmark paper [4] is from 1997), and thus, it might be too early to expect the answer now. Development pipelines show that the number of projects emerging from this new paradigm is steadily increasing and will continue to do so. Attrition rates are alarming, but this is likely to be a consequence of using novel targets and chemotypes, rather than a consequence of employing a chemistry programme from an engineered, serendipitous event (diversity screening) instead of a structure-based idea (rational design).

Furthermore, to improve the otherwise slim chances of success, drug hunters should apply all available options, exploiting HTS and rational design in a parallel and complementary way – there is no reason to rule out either one or the other.

References

1 Eggeling, C. *et al*. (2003) Highly sensitive fluorescence detection technology currently available for high throughput screening. *Drug Discov. Today* 8, 632–641
2 Taylor, P. *et al*. (2002) A standard operating procedure for assessing liquid handler performance in high-throughput screening. *J. Biomol. Screen*ing 7, 554–569
3 Schmidt, E. (2003) Trust me – I'm a doctor. *Drug Discov. Today* 8, 439–438
4 Lipinski, C.A. *et al.* (1997) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* 23, 3-25

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