The optimal fragmentation principle – Reply

Initial letter: Johnson, D.E. (2001) The optimal fragmentation principle. *Drug Discovery Today* 6, 175

Response from Peter H. Bach

Let's make a full meal of IT!

Why only the entrée? Man deserves nutritious meals, perhaps several courses (efficacy, toxicity and metabolism prediction), with the right flavours, using the highest-quality ingredients (would mother want anything less!) from all over the world.

In addition to large pharmaceutical companies providing key inputs, there are other sources of drug development 'ingredients' that could make *in silico* toxicology (IST) work successfully. The regulatory and health agencies have full safety packages in the context of human use and the experience of seeing a big picture. Similarly, the contract research organizations (CROs) have the potential to provide information on many molecules that have failed to go into development because of toxicity. There are already precedents for collaboration between stakeholders who prepare, serve and consume material on which predictive informatics can be based:

- 'DEREK' (Deductive Estimation of Risk from Existing Knowledge) the LASHA (LHASA Ltd, University of Leeds, Leeds, UK; http://www.chem.leeds.ac.uk/luk/) expert system involves corporate members who help address the interests of the companies concerned, based on in-house safety data.
- The Food and Drug Administration (FDA) has shared confidential data in the past with MultiCASE (Beachwood, OH, USA; http://www.multicase.com/).

In addition, the academic community and public domain material has important information and, more relevantly, provides mechanistic insight into pathology lesions. This should enable an additional understanding of where the different processes that lead to the same final toxic end-points (pathology lesion) can affect the accuracy of the prediction.

One burning question for drug developers is 'where should we eat?' Each IST restaurant has a different basis for prediction, which must impart unique strengths and weaknesses. Few individuals would commit themselves to only one restaurant. There should be better ways to access all of the options and select the most appropriate option from any one cuisine when required. The IST industry must find a common platform that will link all the different options (in a user-friendly way) so that rational choices can be made. One possibility is a 'pay as you go' approach (already being offered by i-Tox.com at http://www.i-Tox.com), an associate company of MultiCASE that offers an Internet-enabled *in silico* search system on the basis of pre-paid access. This would increase the use of informatic portals by small companies, who currently can be locked out by expensive licensing agreements. Pay as you IST could also offer the potential for the many small players to add information to the fragment database(s) from their own compounds.

That is all very nice in theory, but chefs rarely part with their best recipes. Industry, CROs and regulatory agencies are bound by commercial interests and confidentiality. The most important challenge is how to convince the *Supremo Chef de Cuisine* (CEOs, Directors, lawyers and accountants) at each stakeholder that sharing information is good in terms of getting safer medicines to the market more rapidly. Corporate moguls (being delicate and far-sighted folk) are likely to be concerned that 'chemical-fragment fruit-salad' could be reassembled to whole fruits, with loss of competitive advantage: not easily reconciled with sharing or common good. Indigestion is the last thing that shareholders would want if their own chemical fragments were used by a competitor to produce a lemon or tangelo (ugli-fruit) for them!

There are many difficult questions for which a consensus is required. The most important question is who would ensure the contents of the Holy Grail on safety are kept safe. Is there a role for a group such as the ICH (International Committee on Harmonisation, Geneva, Switzerland) or ILSI (International Life Sciences Institute, WA, USA) to oversee such a sensitive, but vital development? Will there be a large enough buy-in to make it work? Where does ownership of the different aspects of such an approach start and stop?

The one thing that is more certain is that we will all have to eat out of the same pot. Those who cannot stand the heat in the IST kitchen will not be there when the *pièce de résistance* is served; and it will be served! All of the stakeholders need to start cooking better and safer drugs (rather than just talking about ingredients and flavours) and thinking of swapping recipes. The technology is there to do a good job; the missing ingredient should not be the will to make it happen.

If we do not finish everything on our 'IST plate', mother may decide we should not get dessert, which would be our just deserts for not having tried harder.

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Response from Ann Richard

To follow up on my comment to Dale Johnson and to respond to his entertaining and provocative letter, I confess to some frustration in seeing a show-and-tell of a sophisticated tool for

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