initiative in molecular diagnostics believing that it is intimately coupled with pharmaceutical development, and, being the house that developed Herceptin™, Genentech should know. By emphasizing the similitude of interest between the disciplines, Ross has given us all hope of a new and bright future for a wonderful marriage. We hope it will last.

References

1 Yaziji, H. and Gown, A.M. (2002) Controversies and guidelines in tissue-based HER-2/neu testing in breast cancer.In *Medical Laboratory Observer* (June 2002), pp12–21 (Available online at: http://www.mlo-online.com/ce/pdfs/june02.pdf)

2 Ross, J.S. and Ginsberg, G.S. (2002) Integrating diagnostics and therapeutics: revolutionizing drug discovery and patient care. *Drug Discov. Today* 7, 859–864

Acknowledgement

The author wishes to thank Drs Jeffrey Kant of the University of Pittsburgh, Wayne Grody of UCLA, and Mike Dean of NCI for helpful comments. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government.

Bert Gold
Laboratory of Genomic Diversity
The National Cancer Institute at Frederick
Building 560, Room 11-85
Frederick, MD 21702, USA

Affinity fingerprints – leading the way?

Fingerprint representations are popular tools to search databases for bioactive molecules, and many of these fingerprints are highly diverse in their design [1]. Nevertheless, one way or another, most fingerprints make use of various chemical descriptors to 'indirectly' capture features important for detecting similarities in molecular structure, properties, or biological activity [1]. However, there are exceptions.

Affinity fingerprinting, originally described in the mid-1990s [2], characterizes and compares small molecules based on their binding profiles to reference sets of proteins and is thus experimental and 'direct' in nature. Following this approach, measured binding affinities of a molecule constitute a vector (or affinity fingerprint) in protein reference space, which is conceptually similar to multi-dimensional chemical space defined by a set of descriptors.

In a recent review in *Drug Discovery Today*, Beroza and colleagues described the application of affinity fingerprinting to drug discovery [3]. This approach is now labeled 'chemoproteomics' (using 'biology to inform chemistry'), thereby adding another catchy term to the array of ever so popular '-omics' expressions.

However, the attractiveness of the methodology presented by Beroza *et al*. goes well beyond semantics. Its core component is an iterative procedure during which affinity fingerprints of small training sets of molecules are used to mine databases for similar compounds that are subsequently tested in higher stringency assays, fingerprinted again, and used to identify sets of more active candidate compounds. The authors claim that molecules with low micromolar potency against given targets can routinely be found after a third round of selection, assaying a total of only ~200 compounds. If generally reproducible and transferable, this 'hit rate' would indeed present a substantial advance, when compared with other (fingerprint) methods.

Similar to the situation with many other developments in the chemoinformatics and virtual screening field [1], it is difficult to judge the power of affinity fingerprinting *per se*, because of the absence of published real-life application examples and more extensive comparisons with other methodologies.

However, what about the fundamentals of the approach? Of course, protein reference sets (or, ultimately, a 'surrogate proteome') must be carefully selected, for several reasons. Just to give one example, if specific protein–ligand interactions can be modeled as a linear combination of binding data for two or more unrelated proteins, which is frequently observed [3], then these data must be redundant, at least to some extent, which would perhaps bias lead discovery.

Furthermore, although a major attraction of affinity fingerprint technology is its experimental readout, this very aspect presents a potential problem. To generate affinity fingerprints, compounds typically need to be tested at highest tolerated assay concentration to detect often marginal activity levels (and differences between fingerprints generated in this way are subtle and not straightforward to analyze).

Therefore, the possibility of recurrent non-specific binding events can probably not be ruled out, and the 'activity versus specificity' question could well be of general concern when attempting to apply affinity fingerprints for hit or lead identification. Regardless, these fingerprints add a unique and elegant design to the ensemble of database search tools and the discovery technology established around them deserves attention.

References

1 Bajorath, J. (2001) Selected concepts and investigations in compound classification, molecular descriptor analysis, and virtual screening. *J. Chem. Inf. Comput. Sci.* 41, 233–245

2 Kauvar, L.M. *et al.* (1995) Predicting ligand binding to proteins by affinity fingerprinting. *Chem. Biol.* 2, 107–118

3 Beroza, P. *et al.* (2002) Chemoproteomics as a basis for post-genomic drug discovery. *Drug Discov. Today* 7, 807–814

Jürgen Bajorath
Computer-Aided Drug Discovery
Albany Molecular Research
Bothell Research Center
18804 North Creek Pkwy
Bothell, Washington 98011, USA

  PII: S1359-6446(02)02468-6