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David Gurwitz*
National Laboratory for the Genetics of Israeli Populations and
Abraham Weizman
Laboratory of Biological Psychiatry
Felsenstein Medical Center
Sackler Faculty of Medicine
Tel-Aviv University, Tel-Aviv 69978, Israel
**e-mail: gurwitz@post.tau.ac.il*

Three-dimensional information is not essential for drug discovery ▼

In a recent review in *Drug Discovery Today* [1], Jeff Augen describes the increasing role of *in silico* techniques in the discovery process. The paper is interesting in many respects, including its historical aspect.

However, when describing the drug discovery process, the author seems to exclude the possibility of using a lead discovery strategy when there is no proper structural information on the target of choice. This is emphasized by the figure in the paper, which shows a flow chart of the multiple stages from genomics to clinical trials. The arrows in this figure – and the contents of the paper – seem to suggest that the discovery process is a linear pathway where there is no way to discover new drugs if the protein structure is unknown because this is a required step before moving to the screening stage.

Obviously, HTS is one common strategy to get hits without any knowledge of the structure of the target, which is good because many structures of receptors are yet unknown. Of course, a properly designed library would give better hits than a random one, and the use of three-dimensional (3D) structural information in the design process would increase the odds of getting hits.

Another common strategy, which is complementary to HTS, is property-based drug design, where only the properties of the ligands are used to build predictive models, without any knowledge of the target's structural features. This has been extensively demonstrated by a vast number of QSAR studies (quantitative SARs), where non-structural descriptors are combined to correlate with some observed biological feature (affinity, ADME-related data, toxicity, and so on). Non-structural descriptors (i.e. topological indices, chemical fingerprints, knowledge-based parameters, Lipinski-like 'rules') are also of key importance as rapid filters in a virtual screening process. The nature of these descriptors make them ideal for high throughput elimination of the less favoured constructs among hundred-million member virtual libraries. And, in several cases, this virtual 'screening-out' could result in a library small enough to be synthesized and sent to the HTS automation devices.

This does not change the fact that 3D structural information, when available, is unrivalled for increasing the hit rate by the use of pharmacophoric constraints and/or high-throughput docking calculations. Fortunately, however, for most discovery projects, the undetermined folding of the corresponding protein is not a bottleneck.

Reference

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Roger Lahana
Synt:em
Vice President of R&D
Computational Drug Discovery
Parc Scientifique G. Besse
Nimes, FRANCE
e-mail: rlahana@syntem.com

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