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Commentary

Virtual drug screening for prion diseases: A valuable step?

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The search for effective drugs against transmissible spongiform encephalopathies (TSEs) and other protein misfolding diseases is still a major challenge for those pursuing a therapy for such devastating diseases. The relative inefficacy of all compounds used so far in clinical assays may be due to the lack of knowledge about the relevant molecular target (or targets) for prion diseases and/or different prion strains. Limited pharmacokinetic properties (such as the inability to cross the blood brain barrier), along with significant toxicity also imply that from the hundreds of thousands of compounds investigated *in vitro* for anti-scrapie activity so far, only a few have proven valuable in animal models of TSEs. High-throughput screening of organic compounds for anti-prion activity is time- and money-consuming, as it usually employs as the initial step compound-screening in scrapie-infected cell lines. Effective compounds selected in this step are those that significantly reduce the amount of PrP^{Res} (prion protein resistant to proteases) in these cells after lysis and digestion with proteinase K (Kocisko and Caughey, 2006). Other groups propose that an initial *in silico* step that investigates the drug interaction with the prion protein would improve prediction and selection of most important anti-scrapie compounds based on a PrP binding score (Hosokawa-Muto et al., 2009; Hyeon et al., 2015). In this case, compounds with high binding scores (docking energy) for the highly conserved PrP globular domain will be selected for the following *in vitro* (cell assays and others) and *in vivo* (treatment of infected murine or hamster models) assays.

The work from Daisuke Ishibashi and coworkers proposes a high-throughput docking procedure to funnel the selection of possible anti-scrapie compounds from a huge library of organic compounds (Ishibashi et al., 2016). The group used a structure-based drug discovery algorithm in the DEGIMA supercomputer that allowed rapid selection of prion protein ligands that were further evaluated *in vitro* and *in vivo* regarding their suitability as anti-scrapie drugs. The drug-selection criterion used was binding to the prion protein 'hot-spot' region using, as a reference, the binding affinity of GN8 compound, described by Kuwata and coworkers (Kuwata et al., 2007), in a similar approach as that previously described (Hyeon et al., 2015). This work is substantial for basic research and the clinic as it proposes a virtual screening approach that can then be validated using *in vitro* and *in vivo* assays with prion infected animals. In this case, there is economy of time and costs, as only compounds revealed by the docking simulation that interact with the PrP pocket, previously shown as the binding-site for other anti-scrapie compounds (Kuwata et al., 2007; Ferreira et al., 2014), will be synthesized and further evaluated. Validation of compound interaction with PrP was carried out by surface plasmon resonance (SPR) assays (Ishibashi et al., 2016). In a similar experimental approach, a platform was recently created to unify the docking simulation, MD simulation and quantum chemistry calculations, named NAGARA (Ma et al., 2016). This platform was applied to the discovery of novel *anti*-prion compounds, using as the initial step docking simulations with the globular domain of murine PrP (PDB: 1AG2).

However, one might question whether effective compounds that do not bind to the C-terminal domain of PrP or that have other molecular targets besides PrP (Poncet-Montange et al., 2011) will be excluded from this virtual screening. In the first case, docking with at least the 90–231 domain of the prion protein will prove useful. Besides, if PrP^{Sc} is the target for such compounds, there is an urgent need to address the three-dimensional structure of the most abundant (or repetitive structure) for the PrP^{Sc} aggregates (Requena and Wille, 2014). Molecular dynamics simulations indicated that parallel in-register intermolecular β-sheet architecture can be formed by PrP^{Sc} (Groveman et al., 2014) and the use of a supercomputer (no longer for high-throughput screening) may allow identification of compounds that bind to PrP^{Sc}. That said, this is no easy challenge, and deserves attention from the scientific community, and especially biophysicists and computational

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biologists. Taking into account that the interaction of a compound with a specific region of the prion protein globular domain is a prerequisite for effective anti-scrapie activity (what is not always the case, as discussed above) the work published in *EBioMedicine* provides a straightforward screening approach. In particular, it allows selection of compounds with IC_{50} values in the micromolar range from a library of more than 200,000 molecules. Although effective for different prion strains in infected-cells lines, the selected compounds did not increase survival of prion-infected mice (Ishibashi et al., 2016). This result reinforces the need for a thorough pharmacokinetic assessment of the most promising molecules. In general, this approach by may prove useful to screen for drugs against other diseases, mainly for those with a defined molecular target and a previously characterized binding region in the target protein.

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