Editorial

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Protein Targeted Therapeutics

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Recently D.H. Huller and D Baker from Department of Biochemistry University of Washington described the de novo protein design. Till now proteins were considered as therapeutics and at present they are being tested as targeted therapeutics.

Early work of Paul Ehrlich provided small molecule drugs for the treatment of infectious diseases, metabolic disorders, cardiac diseases, neuromedicine and cancer. Among these were protein drugs like antibodies. More than 20 different antibodies have been approved in Europe and USA [1] as potential pharmaceuticals for pharmaceutical industry.

Engineered knottin peptides (inhibitor cysteine-knots) have generated interest as molecular scaffolds for the development of peptide based pharmaceuticals. Peptides containing a knottin motif are found in a wide variety of animals, plants, and fungi and these can also be produced by a variety of recombinant and chemical synthesis methods. Cysteine knot are small, 4-12 kDa, binding family of ultra-stable polypeptides having a common tertiary fold stabilized by at least three disulphide bonds structure. They hold their structural and functional integrity after exposure to high temperature, proteolytic enzymes, strong acids as well as bases. This enables the oral delivery of these peptides, a major clinical benefit [2]. One of the natural cysteine knot peptide is LINZESS (linaclotide, Allergan/Ironwood Pharmaceuticals), this hormone has been successful in the treatment of irritable bowel syndrome with constipation [3]. Linear and cyclized variants of cysteine knots have been shown to possess similar stabilities. Information about the knottin and cyclic class of proteins is available on the databases http://knottin.cbs.cnrs.fr and http://www.cybase.org.au.

Aaron Chevalier et al. tested Influenza A H1 haemagglutinin (HA) and botulinum neurotoxin B (BoNT/B) as a target for 22660 mini proteins. The researchers generated virtual scaffold libraries with over 4000 backbone geometries in five different topologies HHH, EHEE, HEE, EEHE, HEEH (H-α-helix, E-β strand). Helical segments which binds to HA are HB36.6 and HB80.4 while BoNT/B binds to Synaptotagmin II (Syt 2). For the experimental characterization the researchers selected about 7200 designs against HA and 3400 against BoNT. A substantial fraction of the proteins fold into the designed structures. The design population included the BoNT single disulfides and the HA multiple disulfides. Substitutions at the binding interface and in the protein core were more destructive than substitutions at surface position, and almost all the cysteines were highly conserved in designs containing disulphides. Rosetta designed interactions outside the hotspot regions were found to make important contributions towards the binding and mutations of the non-hotspot HB residues and Ala11, Trp19, Tyr24 showed greatly decreased binding affinity. The effect of these mutations on both binding energy and monomer stability were estimated using Rosetta design calculations and a reasonable correlation was seen between predicted and experimentally determined susceptibility of position mutations.

Summarizing, substitution of designed loop sequences with generic Gly-Ser linkers reduces binding to a greater degree and substituting the designed core residues with valine suggests that loops may play an important role in folding of these proteins. We can say that the de novo protein design has a potential to generate pharmaceutical molecules.

References

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