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Enzyme engineering: An innovative way to manage the economics of biosimilars- Polyclone case study

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Biocatalytic processes are used to synthesize antibiotics and chiral intermediates for pharmaceuticals. There is a major shift in the industry where efforts to convert chemical routes of synthesizing drugs to enzymatic routes is being made. Focus is also on the synthesis of new pharmaceuticals which may require efficient processes for large scale synthesis in the future. Therefore, enzymes are studied more than ever before by pharmaceutical companies that offer them a cleaner and greener approach. Several approaches have been adopted, including screening, engineering, and development of new techniques in reaction systems for different aspects of the enzymes such as improved kinetic properties, stability etc. Polyclone has developed an in silico enzyme engineering framework (eEF) that provides valuable information and has identified key data points for enhanced productivity of economically important enzymes.

eEF identifies potential hotspots in the enzyme that can be used to change the enzyme and attain required function. The hotspots are then used to generates large dataset of permutations and combinations of mutations in the 3D structure of a given enzyme (>200,000) and finally these enzyme modifications are screened by predicting the enzyme activity values such as K_m, K_{cat} etc. The framework utilizes techniques such as Molecular dynamics, Q_M/M_M simulations, Transitions path sampling, Ensemble docking analysis etc., to calculate the activation energy and rate limiting steps of an enzymatic reactions. Recently, a drug discovery protocol- 4D-QSAR methodology was for the first time twigged to accurately predict enzyme activity by utilizing the 3D conformational changes of the E-S complex. Here we use million of data points generated over different E-S simulations called as grid cell occupancy descriptors and identify sensitive regions in the enzyme. These descriptors are further used by different mathematical models to predict kinetic properties of the enzyme. This methodology was tested on a validated set of mutations of serine protease and the test proved to be 83 % accurate. In conclusion, we have designed a protocol that can be used as a screening and selection tool to obtain focused libraries and design novel enzymes.

Biography

In charge of Polyclone's science and strategy, Naveen comes with over 18 years of scientific & entrepreneurial experience in the drug discovery industry across the USA, Australia and India. Prior to his current role in Polyclone, he served as the Director at Philips Research, where he was associated with a portfolio of opportunities for new business creation in healthcare and energy. In his previous roles, he has risen through the ranks - from being a bench worker at an Australian research institute to heading the strategic business unit of an American drug discovery informatics company. He has conceptualized and developed novel solutions for accelerating drug discovery and directed teams consisting of experts from different domains. He has been instrumental in conceiving new ideas that are the basis for Polyclone's patent portfolio.

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