Austin Biomolecules: Open Access

Open Access

Austin Publishing Group

Editorial

Rational Drug Design and Future Directions: Thermodynamic Perspective

Judy E[1], Choudhary S[2] and Kishore N[1]*

[1]Department of Chemistry, Indian Institute of Technology Bombay, India

[2]UM-DAE Centre for Excellence in Basic Sciences, India

***Corresponding author:** Kishore N, Department of Chemistry, Indian Institute of Technology Bombay, India

Received: August 30, 2016; **Accepted:** September 01, 2016; **Published:** September 07, 2016

Editorial

Rational drug design remains a challenge for future in view of diseases which have not found cure as yet. Pharmaceutical industries and academicians have focused their efforts rigorously in this direction. However, the success in many areas has remained marginal [1]. Strategies in rational drug design have recently been reviewed by several authors [2-4]. Development and advancements in rational drug design are dependent on contributions from various fields of science and technology such as molecular biology, molecular biophysics, synthetic organic chemistry, medicinal chemistry, pharmacokinetics and pharmacodynamics to name a few. Taking together a large number of new molecular entities appearing every year, the actual number of compounds which hit the market as drugs are limited due to stringent requirements of Lipinski Rule of Five [5]. Even after successful synthesis of potential new drugs, their target oriented delivery is another challenging task. Literature has extensive information on drug-protein interactions which is both qualitative and quantitative in nature [6]. Understanding physical chemistry underlying drug-protein interactions is extremely important for the reasons mentioned ahead.

Thermodynamic parameters such as binding constant, change in enthalpy, entropy and Gibbs free energy upon binding carry enormous amount of information about the extent of association, as well as the nature of interactions between the drug and the binding site on protein [5]. Identification of the functional groups on potential drug molecules which are responsible for binding to protein is an essential step in rational drug design process. Correlation of the thermodynamic parameters of interaction with the nature of association, and hence the functional groups responsible for interaction is one possible answer in this direction [7].

An insight into thermodynamics of binding interactions in rational drug design over a number of years has led to development of drugs with improved therapeutic efficiencies. Isothermal Titration Calorimetry (ITC) and Differential Scanning Calorimetry (DSC) have proved to be boon for drug development and discovery. Specifically, ITC has guided drug development process based on analysis of the data at least over the period of a decade [5]. A fitting example of such guidance is the evolution of HIV protease inhibitors or statins from the first in class to the best in class [5]. The exothermic enthalpic contribution in the affinity of HIV protease or statins with the respective targets emerged as a major factor in the improvement of the drugs [5]. Minimization of desolvation enthalpic cost should be seriously considered for engineering improved affinity in a drug molecule [5].

The linkage between selectivity and binding thermodynamic profiles has been another important question in rational drug design [8]. Such a linkage has also highlighted importance of enthalpic or entropic contributions in hitting the desired target. Statins, which are marketed cholesterol lowering drugs, act by binding to 3-hydroxy-3-methylglutaryl coenzyme A. An analysis of the binding data on different statins over a period of about 12 years clearly demonstrated significance of enthalpic contribution to the binding free energy and hence emergence of newer class of more effective statins and other drugs [5,9,10].

Importance of thermodynamics in addressing various diseases has been recognized over a period of time. Tremendous amount of efforts have been directed towards genomics, biochemistry, and cell biology of cancer [11] in view of its consequences and significance of treatment. However, its thermodynamic aspects have not been given significant attention. Cancer is a dynamic phase transition from healthy to cancer states or from tumour to metastatic state [12]. Any phase transition is characterized by its thermodynamic properties which could be expressed in terms of enthalpic or entropic contributions.

There have been reports of calorimetry based profiling of blood plasma from colorectal cancer patients [13]. The validation of calorimetry as a diagnostic tool is claimed since this technique could monitor changes in colorectal cancer at different stages of tumour development. The emergence of proteomics in unravelling biochemical changes which give rise to cancer has played a very significant role [14]. Obviously the role of thermodynamics in proteomics which could be applied in the development of prognostic biomarkers and strategies for effective cancer treatment cannot be ignored at any stage. The significance of thermodynamics in cancer stationary states has been highlighted, and entropy generation in cancer evolution has been connected with new possible anticancer therapies [15].

The role of entropy in adhering to the Second Law of Thermodynamics in the living systems in creation and maintenance of structural order is well recognized, and its connection with the heart has also been described [12,16-18]. According to this description, the heart can offset the body's increasing entropic burden by exporting entropy to the surroundings by using its energy. Thus thermodynamic aspects of cardiovascular physiology and heart diseases also need to be addressed. Further, the importance of thermodynamics in modeling brain activity has also been recognized [19]. Well defined laws of

Citation: Judy E, Choudhary S and Kishore N. Rational Drug Design and Future Directions: Thermodynamic Perspective. Austin Biomol Open Access. 2016; 1(1): 1003.

thermodynamics providing relationship between information and energy can certainly be very useful in neuroscience. The application of entropy in context of states of consciousness and associated neurodynamics with specific focus on psychedelic state has been considered [20]. Direct correlation of the First Law of Psychology and Second Law of Thermodynamics has been pointed out [21]. There are many biological processes which have not been addressed based on thermodynamic considerations. One such example is adaptability of blood transfusion and its connection with thermodynamics of the process.

The drug design and development have benefited unquestionably from thermodynamic studies. It has made a big impact in both the academic and industrial sectors. Special emphasis on structural complementarity and optimization of association between the drug and target binding sites are major components of strategies to generate lead compounds [22]. Solubility, selectivity, adsorption, distribution, metabolism, excretion and toxicology are other concerns within restrictions of Lipinski Rule of Five [23]. Major thermodynamic information on such systems has come from calorimetric measurements. The legacy of Prof. Julian M Sturtevant in promoting microcalorimetry to address problems of biological interest has rewarded much more than probably it was thought of [24]. Major challenge for those who employ ITC or DSC in their results is data analysis, which still requires significant efforts in developing more suitable models.

Thermodynamically driven drug design will continue to be important and impactful because it addresses molecular interactions on the basis of energetics and permits bridging connection between structural and thermodynamic information.

References

1. Smietana K, Siatkowski M, Moller M. Trends in clinical success rates. Nature Reviews Drug Discovery. 2016; 15: 379-380.
2. Jones JA, Virga KG, Guminab G, Hevener KE. Recent advances in the rational design and optimization of antibacterial agents. MedChemComm. 2016; advanced article DOI: 10.1039/c6md00232c.
3. Yu C, Niu X, Jin F, Liu Z, Jin C, Lai L. Structure-based Inhibitor Design for the Intrinsically Disordered Protein c-Myc. Scientific Reports 2016; 6: 22298.
4. Gao J, Wang T, Qiu S, Zhu Y, Liang Li, Zheng Y. Structure-Based Drug Design of Small Molecule Peptide Deformylase Inhibitors to Treat Cancer. Molecules 2016; 21: 396.
5. Friere E. Do Enthalpy and Entropy Distinguish First in Class From Best in Class? Drug Discov Today. 2008; 13: 869-874.
6. Klebe G. Applying thermodynamic profiling in lead finding and optimization. Nature Reviews Drug Discovery 2015; 14: 95–110.
7. Thoppil AA, Choudhary S, Kishore N. Competitive binding of anticancer drugs 5-fluorouracil and cyclophosphamide with serum albumin: Calorimetric insights. Biochimica et Biophysica Acta. 2016; 1860: 917–929.
8. Tarcsay A, Keseru GM. Is there a link between selectivity and binding thermodynamics profiles? Drug Discovery Today 2015; 20: 86-94.
9. Ladbury JE, Klebe G, Freire E. Adding calorimetric data to decision making in lead discovery: a hot tip. Nature Reviews Drug Discovery. 2010; 9: 23-27.
10. Kawasaki Y, Sekiguchi M, Kawasaki M, Hirakura Y. Thermodynamic evaluation of the binding of bisphosphonates to human farnesyl pyrophosphate synthase. Chemical and Pharmaceutical Bulletin. 2014; 62: 77-83.
11. Weinberg RA. The biology of cancer, NY, Garland Science: 2007.
12. Paul CW Davies, Demetrius L, Tuszynski JA. Cancer as a dynamical phase transition. Theoretical Biology and Medical Modelling. Cancer as a dynamical phase transition. 2011; 8: 30.
13. Todinova S, Krumova S, Kurtev P, Dimitrov V, Djongov L, Dudunkov Z, et al. Calorimetry-based profiling of blood plasma from colorectal cancer patients. Biochimica et Biophysica Acta. 2012; 1820: 1879-1885.
14. Dias MH , Kitano ES , Zelanis A , Iwai LK. Proteomics and drug discovery in cancer. Drug Discovery Today. 2016; 21: 264-277.
15. Lucia U. Thermodynamics and cancer stationary states. Physica. 2013; 392: 3648-3653.
16. Prigogine I. From being to becoming: Time and complexity in physical sciences. San Francisco: Freeman WH. 1980.
17. Dini FL, Guarini G, Morrone D, Marzilli M. The second law of thermodynamics and the heart. Future Cardiology. 2012; 8: 697-706.
18. Uehara M, Sakane KK, Bertolotti SA. Thermodynamics of the heart: Relation between cardiac output and oxygen consumption. American Journal of Physics. 2008; 76: 566-569.
19. Collell G, Fauquet J. Brain activity and cognition: a connection from thermodynamics and information theory. Frontiers in Psychology. 2015; 6: 818.
20. Carhart-Harris RL, Leech R, Hellyer PJ, Shanahan M, Feilding A, Tagliazucchi E, et al. The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs. Frontiers in Human Neuroscience. 2014; 8: 20.
21. La Cerra P. The First Law of Psychology is the Second Law of Thermodynamics: The Energetic Evolutionary Model of the Mind and the Generation of Human Psychological Phenomena. Human Nature Review. 2003; 3: 440-447.
22. Henry CM. Structure based drug design. Chemical Engineering News. 2001; 79: 69-74.
23. Garbett NC, Chaires JB. Thermodynamic studies for drug design and screening. Expert Opinion on Drug Discovery 2012; 7: 299-314.
24. Sturtevant JM. Some applications of calorimetry in biochemistry and biology. Annual Review of Biophysics Bioengineering. 1974; 3: 35-51.

Citation: Judy E, Choudhary S and Kishore N. Rational Drug Design and Future Directions: Thermodynamic Perspective. Austin Biomol Open Access. 2016; 1(1): 1003.