Editorial

Systems and Network Biology in Pharmaceutical Drug Discovery

Cancer is appreciated to be a 'Systems Disease' harboring a circuitry that is often times more complex than that of advanced computers [1]. In most malignancies', there is a common underlying robustness in this circuitry that is found to resist to any changes such as that induced by perturbations from drugs [2]. It is being recognized that cancers emanate from aberrations in multiple signaling molecules that cannot be successfully targeted by a drug designed to hit a single pathway [3]. On the other hand, in instances where combination therapies do work to some extent, the development of acquired resistance and ensuing tumor recurrence results in minimal success or even complete treatment failure [4]. Cancer drug resistance results from genetic i.e. gene-gene, protein-protein (PPI) interaction- or epigenetic i.e. arising from non-coding microRNA-mRNA interaction networks. This is further complicated by tumor heterogeneity and the emerging acceptance of the presence of a sub-population of cancer stem cells (CSCs) that do not respond to most commonly used chemotherapeutic or targeted combination regimens [5]. Collectively, these multifocal hurdles pose limitless challenges to drug industry and are considered the underlying reason for the high drug attrition rates in pharmaceutical industry. The alarming rise in the cost of drug development together with ever increasing global cancer burden clearly points to the need of newer strategies if one needs to conquer this multifaceted disease.

Large scale genomic analyses of cancer patient cohorts have become routine in cancer diagnostics. Additionally, the genome wide association studies (GWAS), next generation RNA sequencing and fragment analysis is heavily being employed to identify biomarkers specific to different cancer types. Nevertheless, these approaches are reductionist in nature and focus on the identification of single or a set of so called druggable markers. The realization that cancer networks cannot be fully deciphered using reductionism has led researchers to shift their focus to holistic 'Systems Biology' approaches [6]. Systems biology is the study of interactions within the biological system and is an interdisciplinary area research that is heavily dependent on mathematics and network modeling. Thanks to advancements such as systems and network pharmacology, researchers can now perform simulations and model the circuitry of tumors to identify weak nodes in cancer that can be successfully attacked using novel drugs or their combinations [7]. Systems and network approaches have been applied to identify biomarker network for early diagnosis and are now being used to predict the outcome of clinical trials early on [8]. These computational advancements are rapidly cementing their position in mainstream cancer research and are expected to play pivotal role in cancer research in the immediate future.

The primary thought process while developing this thematic issue was to keep researchers abreast with the latest developments in computational biology areas benefitting cancer research and drug discovery. Therefore, I organized this volume covering a wide range of systems and network related research topics from expert computational systems biologists. As the readers will appreciate, the ten articles in this thematic issue are quite diverse and cover the most burning areas in cancer systems biology.

The thematic issue starts with a review from Dr. Susmita Datta's group (University of Louisville, USA) on the use of differential network analysis in human cancer research. This article provides a statistical test to detect network topology and connectivity scores on differentially expressed genes in different liquid tumor models [1].

A review from Dr. Dimitrios Roukos (Greece) and colleagues comprehensively describes how next generation sequencing and network biology can aid in the rational design of effective therapies in cancer. The readers can gain knowledge of the latest developments in the application of next-generation sequencing and patient's whole genome analysis for personalized treatment using available drugs and the discovery of next-generation drugs based on genome science and network biology advances [2].

This is followed by an article from Dr. Tero Aittokallio's group (Finland) that provides deep insights into network pharmacology approaches for the design of multi-targeted approaches in cancer. Their article provides representative examples of how network-centric modeling may offer systematic strategies toward better understanding and even predicting the phenotypic responses to multi-target therapies [3].

In another review, Dr. Jean Clairambault's group (INRIA, France) presents a very interesting perspective on physiologically based mathematical models to optimize therapies. Using a colorectal system, the authors discuss differential equation based pharmacokinetics-pharmacodynamics models for the main cytotoxic drugs used in the clinic and also advocate simultaneously designing models of the proliferating cell populations under therapeutic control [4].

In the next article, Dr. Sheng Ce Tao (Shanghai Jiao Tong University China) discusses how protein microarrays studies are helping researchers understand drug mechanisms and biomarker discovery. Some very new concepts in proteome microarrays for large scale identification of protein-protein interactions to lectin microarrays for live cell surface glycan profiling, with special emphasis on their use in studies of drug mechanisms and biomarker discovery [5].

In her review, Dr. Muqbil (AMU, India) and colleagues discuss a holistic new form of nuclear export inhibition therapy that simultaneously targets nuclear retention of multiple tumor suppressors. The review provides solid rationale for the application of computational tools, particularly pathway analysis to fully elucidate the consequence of global reorganization of hundreds of tumor suppressor proteins in cancer and normal cells. The review also provides insights into the use of pathway tools to evaluate synergistic drug pairs to enhance the activity of nuclear transport drugs [6].

Investigating one of the most burning topics in oncology, in her review, Dr. Christel Herold-Mende's group (Heidelberg Germany) discusses the high-throughput and top-down systems biology analyses on cancer stem cells. The authors present the fundamental concepts of systems biology as well as its applications for glioma stem cell research [7].

In our review (Wayne State, USA), we present the case for the use of systems biology and network modeling in the detection, prevention and treatment of pancreatic cancer. Our article discusses the advantages of systems biology over traditional methodologies for this incurable disease. We provide a case scenario for rationally combining drugs based on network derived knowledge [8].

This thematic issue carries two research articles as well and serve as proof of concept for the preceding 8 reviews. In the penultimate research article Dr. Zhiwei Wang's group at Harvard presents proteomic-based analysis for identification of proteins involved in 5-fluorouracil resistance in hepatocellular carcinoma [9].

Finally, Dr. Amir Abdollahi (Heidelberg, Germany) presents his research article (featured on the cover of this thematic issue) deciphering the systems biology of mTOR inhibition using integrative transcriptome analysis. The article provides pathway network analysis and biological validation of the mTOR inhibitor induced reversal of angiogenic process in different cancer cell line models [10].

Collectively this thematic issue covers some of the most burning areas of research related to cancer systems and network biology. It was indeed a great pleasure to collect these ideas from experts in the domain of computational biology. The articles carry more than a thousand updated references that would certainly serve as excellent reading resource for researchers working in this field. I hope that this thematic issue will be well received and make for an interesting reading.

ACKNOWLEDGEMENTS

First and foremost, I would like to thank the Editor-in-Chief Dr. William A. Banks for giving me the opportunity to organize this special theme issue. I would like to thank all of the contributing authors for their outstanding articles. I also would like to especially acknowledge all of the anonymous reviewers who kindly reviewed the articles. Dr. Frances WJ Beck's assistance in arranging peer review and proof reading the manuscripts is deeply acknowledged. I am indebted to the Editorial Director Mr. Mirza Kazim Ali Baig and the staff members of Bentham Science Publishers for their assistance in coordinating the publication of this special issue in the journal *Current Pharmaceutical Design*.

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