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editorial

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Can network pharmacology rescue neutraceutical cancer research?

Advances in systems and network biology have revealed a phenotypic robustness in the cancer network structure. It is needless to say that the removal of individual components using single pathway targeted drug from such networks has surprisingly little functional consequence [1]. Additionally, the intra-tumor heterogeneity observed in most of the complex malignancies indicates that it is extremely unlikely that drugs that target a single protein/pathway would be active against the majority of tumor cells [2]. Rather than targeting a single entity, the renewed appreciation of developing network-directed drugs is an intense area of research. Newer concepts such as 'Network Pharmacology' are being investigated, in which holistic driving principles are being applied to explain that the efficacy of a candidate drug is the result of its cumulative effect on intended and secondary/off targets. Such systems and network biology-based developments have been purported to help in expanding not only the current opportunity space for druggable targets, but also in reducing attrition during drug development. Nevertheless, these advances have not been applied to enhance the scope of neutraceutical cancer research (diet-derived agents that are relevant to cancer research); a field suffering from criticism in an environment where multi-targeting strategies for drug development are becoming more widely accepted.

For centuries, neutraceuticals, especially phytochemicals, have been investigated for their medicinal benefits and in the past few decades their supposedly anti-cancer effects have attracted a lot of attention [3]. A Pubmed search (on April 25th) using the keywords *natural agents* and *cancer* returns ~10,000 hits. Numerous laboratories worldwide have investigated different classes of dietary compounds for their cancer preventive and therapeutic benefits and a few of these agents have even entered into the clinic [4]. To date, however, no single unifying mechanism of action has been proposed for their observed cancer selective effects. A single agent (for example, the red wine polyphenol, resveratrol) has been shown to be an indirect Sirtuin1 inhibitor in one laboratory whereas an anti-oxidant in another and even an oxygen radical generator elsewhere [5]. Natural agents can potentially modulate every type of biological molecule and similarly may be able to hit a range of biological networks. In a way it is somewhat perverse that the diffuse and weakly pleiotropic mechanisms of neutraceuticals have drawn harsh criticism in an era when the pharmaceutical industry is pursuing network theories to explain the benefits of developing promiscuous agents. Indeed, the fault lies in

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neutraceutical researcher's approach that have somewhat failed to take advantage of these technologies to provide deep mechanistic evidence supporting such multi-targeted observations. Compounding this, most of the laboratory investigations on neutraceuticals have been performed at physiologically irrelevant high doses that cannot be translated into the clinic due to their poor bioavailability. These issues pose two important questions: (a) are the multi-targeted effects of neutraceuticals sufficiently significant to impact cancer and, hence, worthy of being incorporated in mainstream preventive and therapeutic strategies?, and (b) are we really using the precise pre-clinical models and appropriate technologies to investigate these agents in a holistic manner?

Lack of target-specificity has been a frequently voiced criticism of natural compound or natural compound-derived synthetic analogues, even when a drug development approach using a 'one drug-one target' philosophy has largely failed. Therefore, multi-targeting concepts, such as systems pharmacology, polypharmacology and network medicine (multi-targeting approach) for the treatment of complex diseases such as cancer are emerging hot topics in both industry and academia. These innovative concepts are being applied to the development of medicines for treating cancer. Among many examples, the multi-targeting effects of older agents, such as aspirin and metformin are beginning to emerge, which is consistent with network pharmacology philosophy. In our view, the ability to target multiple pathways is a desirable attribute for novel agents because the pathogenesis of cancer is complex and often characterized by dysregulation of multiple genetic/signaling pathways. Therefore, agents selective against a single pathway/molecule may have limited clinical utility. This prompted us to consider the philosophy of polypharmacological approaches (also known as multi-targeting drug discovery approach). In keeping with this philosophy, our view is that nutraceuticals would serve as a novel multi-targeting agent which would specifically target heterogeneous population of cancer cells that are morphologically and molecularly distinct.

The emergence of systems and network biology in the post human genome project era has enhanced our knowledge of multi-pathway interactions in cancer that, in turn, has been aided by greater understanding of the mechanism(s) of action of drugs [6]. Systems biology has shifted the dogma from reductionism to holism, and, as a biology-based inter-disciplinary field, focuses on studying interactions in biological systems. It is an amalgam of many disciplines, such as Phenomics, Genomics, Epigenomics, Interactomics, Metabolomics, Transcriptomics and so on, that have collectively laid the foundation of the field of network pharmacology that is solidifying its position in cancer medicine. Network pharmacology invokes the idea that to have an effect, drugs must be designed to target multiple avenues in cancer (i.e. the entire aberrant network or weak nodes within the network). Additionally, unlike earlier concepts where off-target effects were always pooled as side effects, through network pharmacology, it has been demonstrated that secondary drug interactions or promiscuity, such as that observed with neutraceutical agents, often engages a synergistic combination of the appropriate molecular targets in cancer cells to produce treatment success. Therefore, it serves as an excellent platform to investigate the promiscuity of neutraceutical actions against cancer cells. Among the various applications of network pharmacology include, in the identification of weak nodes in global cancer networks, predicting drug toxicity, drug repurposing and identifying multi-scale mechanisms of drug action and in the rational design of potent anti-cancer drug combinations [7]. On the basis of its potential and ever evolving applications, this technology has been proposed to become a major player in future cancer drug discovery and certainly has the potential to benefit natural agent research [8].

Unfortunately, the much-needed science of network pharmacology has not been applied to neutraceutical research. Such investigations are extremely important, because most natural agents invariably influence more than one target, either (a) as a consequence of structural similarities between the intended target and their downstream pathways, (b) through allosteric effects on secondary targets, (c) through pleiotropic mechanisms, where an interaction results in multiple downstream effects on adjacent genes/proteins or even on miRNAs, or (d) through multivalent target binding by different presentations of the active molecule. Also, most of these agents have been shown to synergize with chemotherapeutic drugs. Such complex interactions cannot be investigated using traditional molecular biology tools. Rather, high-throughput systems and network technologies are needed that would take into account the global and multi-scale changes induced by these multi-targeted agents. Because cancer networks typically relate directly to systems-level function or dysfunction, studying such combinatorial impact of neutraceuticals is predicted to improve molecular understanding.

So, how can network pharmacology rescue neutraceutical cancer research? What is the blue print for such investigations and where to begin? Indeed performing multi-scale analyses that study neutraceutical-induced network changes in the genome, epigenome, proteome, kinome, miRNAome and transcriptome is time-consuming and requires a huge capital investment. Moreover, each tier of molecular organization holds equal weight and none can be ignored, and below are some suggestions that may possibly make the process cost-effective and less time-consuming. First of all, the test systems should involve pharmacologically relevant doses of the agent(s) and not *supra* concentrations that are not clinically translatable. Secondly, the experiments should be designed to encompass biologically meaningful time points that capture early signaling changes. One has to incorporate suitable normal cell models that would cut down the risk of investing in any agent that demonstrates adverse reactions on healthy cell network. Finally, a very cohesive interaction between biologists and computational researchers (bioinformaticist and network biology researchers) is absolutely necessary. Nevertheless, these are only peripheral suggestions, and as we have learned from initial outcomes, more robust experimental design can be incorporated.

The past decade has witnessed tremendous increases in the interactions between interdisciplinary fields of research. In the drug discovery arena, researchers are increasingly appreciating the value of 'omic' technologies to improve candidate drug development [9]. Network pharmacology has brought a paradigm shift in our understanding of drug action where 'promiscuity' not chastity is the buzz word for the treatment of genetically heterogeneous malignancies that are not amenable to single pathway targeted drugs [10]. To that end, nutraceuticals are the most well-known promiscuous (multi-targeting) agents that hold promise for cancer

prevention and treatment. Therefore, why the same principles are not being applied to the study of nature's arsenal of pleiotropic agents is worth questioning. Unfortunately, proponents of neutraceutical research have shown hesitation in embracing these emerging technologies that hold the potential to scientifically predict and prove the clinical worthiness of natural agents. It is up to the research community how it utilizes a new concept 'Neutra-Network Pharmacology' to rescue this important area of research. We need scientists who will not hesitate to embark on paradigm-shift research because only such high-risk research will yield greater benefit to those suffering from the devastation of cancer.

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