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Editorial

Theme Section on Cancer Chemoprevention

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Cancer chemoprevention is an active area in cancer research. Work is under way in research laboratories around the world to tackle challenges such as finding the right molecular targets, biomarkers and animal models for predicting efficacy of chemopreventive compounds for human cancers and translating our basic research into clinical cares. The other challenge is to disseminate the findings into the larger biomedical and pharmaceutical community to enable the translation of concepts into therapeutic products. This theme section was organized in response to an invitation from *Pharmaceutical Research* to highlight the latest advances in cancer chemoprevention research.

It has been known for a while that dietary factors have an impact on age related diseases including cancer, cardiovascular and central nervous system (CNS). These phytochemicals typically transduce different cellular signaling pathways to effect proteins/receptors/enzymes functions directly or indirectly via modification of gene transcription and/or mRNA stability leading to modulation of proteins/receptor/enzymes levels and their subsequent pharmacodynamic effects *in vivo*.

Cancer is a very complicated disease with multi-factorials including gene mutations, viral infections, environmental factors, abnormal expressions of pro-growth and/or decreased level of pro-apoptotic proteins. Bharat B. Aggarwal's group reviews the various factors influencing cancers in human and how we can prevent against cancers through possibly major lifestyle changes in some of the more obvious as well as not so obvious factors. Hasan Mukhtar's group presents an interesting result on the suppression of NF-κB and its regulated gene products by oral green tea polyphenols in his well established genetic TRAMP (transgenic adenocarcinoma of the mouse prostate) mice prostate cancer model in cancer chemoprevention. Using similar TRAMP mice prostate cancer model, Barve *et al*. showed that dietary curcumin or PEITC alone or in combination, significantly decrease incidence of prostate tumor formation with decrease proliferation and increased apoptotic index as well as down-regulation of Akt signaling pathway.

Shivendra Singh's group examined the role of reactive oxygen species (ROS) on the induction of signaling and apoptosis by plumbagin, a constituent of the widely used medicinal herb *Plumago zelanica* L. in human prostate cancer cells. They found that plumbagin treatment decreased viability of prostate cancer cells, irrespective of their androgen or p53 status, and this were accompanied by ROS production, depletion of intracellular GSH levels and that pretreatment of cells with the antioxidant NAC inhibited plumbagin-mediated ROS generation and apoptosis. Rajesh Agarwal's group investigated the growth inhibitory property of silibinin, a compound found abundantly in grape seeds, on the impairment of constitutively active TGF-alpha-EGFR autocrine loop in human prostate cancer cells. Mukhtar's group contributed their second article in this Theme Issue by examining carnosol, a dietary diterpene, which displays growth inhibitory effects in human prostate cancer cells leading to G2-phase cell cycle arrest and targets the 5′-AMP-activated protein kinase (AMPK) signaling pathway, which was discovered using a 638 protein-array. The results from this study may open the door to new area of research in cancer chemoprevention.

Marilyn Morris studied the inhibitory effects of biochanin A (BCA), a commonly found bioflavonoid polyphenolic compound using human MCF-7 breast cancer tumor in a murine xenograft model. Treatment with the mixture of BCA, qucercetin and EGCG at doses of 5 mg/kg produced similar effects as seen with 15 mg/kg BCA. BCA may represent a breast cancer preventive agent, either administered alone or in combination with other flavonoids. Fazlul

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Sarkar's group reported the chemopreventive potential of diindoylmethane (DIM), a metabolite of indole-3-carbinol, found abundantly in cruciferous vegetables in pancreatic cancer cells. They found that DIM caused cell growth inhibition and apoptosis and pretreatment sensitized the cells to cytotoxic action of chemotherapeutic drug gemcitabine through up-regulation of Par-4 (prostate apoptosis response-4), which is a unique pro-apoptotic protein. CV Rao's group reported the chemopreventive potential of oleanolic acid (ONA) and its analog 18-alpha-olean-12-ene-3-beta-23,28-triol (OT) in AOM-induced colonic aberrant crypt foci (ACF). They also found that OT possesses anti-inflammatory properties in that it blocked COX-2 expression in HT-29 cells and suppressed iNOS activation in RAW264.7 macrophages. Munday *et al*. studied the structure–activity relationship and organ specificity in the induction of GST and NQO1 by alkyl-aryl isothiocyanates (ITCs). They found that *in vivo*, the urinary bladder was the most susceptible organ with –alpha-methylbenzyl ITC and cyclohexymethyl ITC being the most effective. Last but not least, Ming Hu's group presented works on the intestinal absorption mechanisms of prenylated flavonoids found in heat-processed epimedium koreanum Nakai (Yin Yinghuo, YYH) using Caco-2 cell model and perfused rat intestinal model. In the perfused rat intestinal model but not in Caco-2 cell model, prenylated flavonoids with a glucosidic bond were rapidly hydrolyzed into corresponding metabolites. Overall, they found that poor bioavailability of prenylated flavonoids present in heat-processed YYH results from their poor intrinsic permeation and transporter-mediated efflux.

We are hopeful that the readers will find valuable information in the different contributions of this theme section and in addition, these will help them formulate new ideas, design and execution of innovative and challenging experiments as related to cancer chemoprevention research.

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INTERVIEW QUESTIONS FOR DR TONY KONG

1. What do you think holds the key to your success as a pharmaceutical scientist?
   Response: I think the keys to be successful as a pharmaceutical scientist are to have excellent training both at the Graduate student and post-doctoral levels, wonderful mentors and collaborators, superb students and post-docs and stimulating environment to work.
2. What do you consider to be your key research accomplishments?
   Response: About 15 years ago, very little study was done in understanding how phytochemicals in particularly natural occurring dietary cancer chemopreventive compounds trigger cellular signal transduction leading to gene expression and their pharmacodynamic effects. My lab was one of the first labs to demonstrate these effects and subsequently many laboratories joined in to study signal transduction trigger by phytochemicals.
   1. understanding the complex interactions between phytochemicals and the biological cellular and molecular system in terms of cellular signal transduction and gene expression profiles.
   2. elucidating the signaling pathways and pharmacogenomics of two classes of dietary cancer chemopreventive compounds (isothiocyanates found abundantly in cruciferous vegetables and polyphenolic compounds such as curcumin and green tea) leading to their *in vitro* and *in vivo* pharmacodynamic responses in prevention of cancers and other chronic inflammatory diseases.
   3. studies of drug metabolism, pharmacokinetics, pharmacogenomics and pharmacodynamics of cancer chemopreventive compounds *in vivo*.
   4. the role of transcription factor Nrf2 in the development of colon, skin and other cancers in the transgenic knock-out mouse models
   5. Nrf2 and inflammatory interactions in many diseases including cancer and chronic inflammatory diseases.
3. What was the turning point in your career?
   Response: Probably my post-doc trainings at the NIH.
4. Who are the individuals who most influenced your research career?
   Response: Bill Jusko my Ph.D. mentor in Buffalo, Dan Nebert, Rick Klausner and Larry Semelson my post-doc mentors at the NIH.
5. Pharmaceutical scientists are faced with the dilemma of having to publish in biomedical or basic science journals. Does it mean cutting edge science will not likely be featured in the Pharmaceutical Research?
   Response: I think this is a good thing. Pharmaceutical scientists have to push the frontier to publish in high impact biomedical and basic science journals and at the same time using the same technologies to publish in Pharmaceutical Sciences journals such as *Pharmaceutical Research*, which will certainly bring up the science and the impact factor of Pharmaceutical Sciences journals. For example my lab has been publishing in *Cancer Research*, *Trends in Pharmacological Sciences*, *J. Biol. Chem*. as well as Pharmaceutical Sciences journals including *Pharmaceutical Research*, *J. Pharm. Sci*. and *AAPS J*. This cross-interdisciplinary of published work will tend to expand the reading audience.
6. Where is the field of Cancer Chemoprevention, and how do the articles in the theme section fill the gap?
   Response: The field of Cancer Chemoprevention is a fast growing field especially with National Cancer Institute's (NCI) new initiatives that to cure cancer, we would need to start with prevention, including chemoprevention for high risk individuals. Many of the authors of the articles in this theme section published in high impact journals such as Cancer

Research, but due to the limited space, our theme issue has captured some of these articles. Importantly, bringing together all these cancer chemoprevention researchers' works under the same issue, it will certainly increase the impact of the field and the articles.

7. What are the challenges for cancer chemoprevention and how can they be overcome?
   Response: The major challenges for cancer chemoprevention is translating to the human patients, creating better and more predictive animal models, surrogate/biomarkers (genes) markers for human cancers and more efficient drug discovery and development of chemopreventive compounds for human use. NCI has made a push to make chemoprevention more translational, as such clinical studies encompassing the latest know-how of some of these compounds are being conducted. Better and more predictive animal models, biomarkers (genes) would need to be improved and enhanced for translational purposes. More effective compounds as well as enhanced delivery systems would be needed. In terms of personalized medicine, genotyping and phenotyping of functional SNPs (single nucleotide polymorphism) as well as other high risk factors such as viral infections in driving cancer development would be necessary.
8. What is the key to developing successful collaborative relationships?
   Response: In today's scientific endeavor, collaboration is one of the key to successful execution of a project or manuscript. Create an atmosphere with the collaborators that the collaboration is mutually benefit rather than competitive, both sides offer unique skill sets and importantly the trust factor is essential with close personal relationships.
9. What is your philosophy of educating graduate students?
   I have taken two prone approaches on this subject matter. First I advise my students to learn biology in-depth due to the rapid integration of cellular and molecular biology into many research projects and environments. Secondly, I also insist that my students be well grounded in the basic pharmaceutical sciences such as pharmacokinetics (PK), pharmacodynamics (PD) and drug metabolism (DM) (PPDM). With these foundations, they could perform cutting-edge research.
10. What are the challenges facing the pharmaceutical sciences?
    There are many challenges facing pharmaceutical sciences, particularly in pharmacy schools setting. Some of these are global scientific, and others are institutional. In terms of institutional, many of our young faculty in pharmaceutical sciences spends a great deal of time teaching Professional Pharmacy courses as well as graduate courses, which limit their time and effort in performing state-of-the-art research. In terms of global scientific, there are still major challenges from drug delivery to PPDM in pharmaceutical sciences. New methodologies in predicting PK/PD of drug efficacies and/or toxicities, new *in vivo* imaging technologies, personalized medicine, and integration of pharmacogenomics, biomarkers in predicting drug efficacies/toxicities.
11. What is the place for collaboration with industry in academia?
    There are several ways that academia faculty could collaborate with industry. For instance, academia can offer certain unique technologies and/or service contracts that industry could utilize and performing contractual research in academic settings. Secondly, I think industry won't mind to offer "grants support" to fund certain number of graduate fellowships to train our graduate students, the next generation of pharmaceutical scientists.

Ah-Ng Tony Kong is Professor II and Glaxo Professor of Pharmaceutics at Rutgers—The State University of New Jersey and the Director of the Graduate Program in Pharmaceutical Science. He received his B. Pharmacy from the University of Alberta, Canada, and his Ph.D. in Pharmaceutics/Pharmacokinetics from the SUNY Buffalo. He did postdoctoral research at the National Institutes of Health (NIH), Bethesda, MD. He joined the faculty at Thomas Jefferson University (1991) and the University of Illinois at Chicago (1995). He moved to Rutgers in early 2001. Dr. Kong's research efforts focus on the cellular signaling, gene expression/genomics, pharmacokinetics/drug metabolism and in vivo cancer chemoprevention using various animal cancer models by naturally occurring dietary phytochemicals. His discovery in mid 1990s that these phytochemicals activate MPAK signaling, Nrf2, a master regulator of anti-oxidative stress and regulate gene expression opened new frontier for their research towards diseases prevention and treatments in cancer as well as in cardiovascular, metabolic and CNS diseases. Dr. Kong's research has been supported by several NIH grants. He was the recipient of the 1994 Young Investigator Award in Pharmacokinetics, Pharmacodynamics and Drug Metabolism (PPDM) from the American Association of Pharmaceutical Scientists (AAPS) and was elected a Fellow of AAPS in 2004. Dr. Kong is an Editor (2004–present) of *Pharmaceutical Research* and on the Editorial Boards of *Biopharmaceutics and Drug Disposition*, *Archives of Pharmacal Research*, *Acta of Pharmacologica Sinica* and the *Chinese Journal of Pharmaceutical Sciences*. He has chaired and given presentations in many National and International Symposia. He is a member of the NIH study sections since 1999. He teaches in Biopharmaceutics, Pharmacokinetics and Drug Metabolism to the PharmD and Ph.D. Students at the Ernest Mario School of Pharmacy.