**Research from Professor Ah-Ng Tony Kong’s Laboratory**

Professor Kong’s current research involves Pharmacodynamics of dietary phytochemicals; Cancer interception/prevention by dietary phytochemicals, botanical products, and drugs/repurposed drugs; Human pharmacokinetics (PK)/pharmacodynamics (PD) studies and PKPD modeling and simulation; NRF2-mediated Redox Signaling; Mitochondrial metabolic and epigenetic reprogramming in diseases and phytochemicals/drug treatments. The impact of Professor Kong’s research reflected by more than 300 publications with a total citation of more than 36,000, H-Index of 109 and trained more than 80 doctoral students, postdoctoral associates, and visiting scholars with 30 NIH R01 grants being funded to date.

---

**Cancers are Preventable Diseases: Cancer Prevention by Dietary Phytochemicals and NSAIDs**

Cancer development generally involves multi-stage processes including initiation, promotion and progression (scheme below). In human, depending on the organs/tissues, cancer takes between 10 to 50 years from the initiation stages to diagnosable stages and to advanced metastisized stages of tumors. Evidence suggests that ~80% of human cancers are linked to environmental factors impinging upon genetics/epigenetics. Recent evidence suggests that adults younger than 50, there is an increase in overall cancer incidence from 1995 to 2020 (*CA Cancer J Clin*. 2024;74(1):12-49). This implicates that high risk exposure to environmental factors such as dietary factors, among others, in earlier years (eg in their 20s), would see an increase cancer rates in their 30s or 40s.


---

**Schematic representation of multi-stage carcinogenesis**
Exposure to intrinsic/extrinsic factors, including various toxic chemicals, oncogenes, viruses (e.g., HBV, hepatitis B virus), ROS/RNS, and inflammation, can resulting in genetic mutations and/or epigenetic alterations that cause the initiation of carcinogenesis in normal cells. The initiated cells and non-neoplastic cancer stem/progenitor cells can first progress to benign tumors, which would be amenable with surgery, radiation and or chemotherapy, if detected early, with subsequent progression to advanced/metastasized/malignant/drug-resistant tumors due to the prolonged effects of chronic inflammation, various irritants and aberrant hormones. Advanced/metastasized/malignant tumors are typically very difficult to treat since they are resistant to radiation and chemotherapy. Hence it is critically important to **PREVENT** cancers from progressing to the latter stages.

**Schematic representation of cancer chemoprevention strategy using dietary phytochemicals and non-toxic therapeutic drugs**

Oxidative stress, inflammation and reactive intermediates of carcinogens can cause genetic mutations and epigenetic alterations. Through the promotion/progression stages, initiated cells become advanced/metastatic tumor cells. Applying dietary phytochemicals at the early stage of carcinogenesis may block further development of carcinogenesis. Treatment with dietary phytochemicals and/or relatively non-toxic therapeutic drugs on cancer cells may induce positive results, including autophagy, cell cycle arrest, apoptosis, and differentiation, and may block tumor development.

**Cancer Prevention by Dietary Phytochemicals via NRF2-signaling Pathway**

As discussed above, cancer is driven by a series of genetic/epigenetic changes in tumor suppressor genes and oncogenes impacted in part by oxidative stress, inflammatory signals, among others. The concept of epigenetics has been defined as “the study of heritable changes in gene expression that occur without a change in DNA sequence” (Wolffe et al., 1999). In cancer, epigenetic hypermethylation of the promoter regions of certain tumor suppressor genes is thought to be the most relevant epigenetic change associated with malignant transformation. These heritable changes occur through the methylation of cytosine bases in the DNA and by post-transcriptional modifications of histones (Baylin et al., 2000).

Environmental factors, diet and lifestyle have an impact on the development of various cancers in humans. Hence, minimizing exposure to environmental carcinogens, maintaining a healthier lifestyle (e.g., exercise) and consuming a healthy diet are thought to be reasonable approaches for cancer prevention. In addition to genetic mutations, epigenetic alterations play an important role in cancer development. It is believed that epigenetic changes arise before genetic alterations. The potential of dietary phytochemicals as cancer chemo-preventive/anti-cancer agents through epigenetic modification has been demonstrated in many studies.


Dietary phytochemicals like sulforaphane, curcumin, triterpenoids, among others would drive epigenetics reprogramming potentially resulting in cancer and health protection.

References:

Pharmacodynamics of curcumin as DNA hypomethylation agent in restoring the expression of Nrf2 via promoter CpGs demethylation. *Biochem Pharmacol*. 2011


Biological redox signaling plays an important role in many diseases including cancer (Redox Signaling, mitochondrial metabolism, epigenetics and redox active phytochemicals. *Free Radic Biol Med.* 2022). Recent evidence suggests that reactive oxygen/nitrogen species (RO/NS) modulate epigenetic machinery driving gene expression. RO/NS affect DNA methylation/ demethylation, histone acetylation/deacetylation or histone methylation/demethylation. Many health beneficial phytochemicals possess redox capability that counteract RO/NS either by directly scavenging the radicals or via inductive mechanism of cellular defense antioxidant/reductive enzymes. Amazingly, these phytochemicals also possess epigenetic modifying ability. Graphical presentations as summarized below.
Recently, Professor Kong’s lab integrated research on mitochondrial metabolic rewiring, epigenetic reprogramming, transcriptomic gene expression and redox activators dietary anticancer phytochemicals to better understand cancer progression and prevention/treatment. We found that redox signaling plays an important role in the rapid metabolic rewiring of critical metabolic pathways including the tricarboxylic acid (TCA) in sensing the cellular microenvironment redox status by rewiring some of the metabolites including Acetyl Coenzyme A, α-ketoglutarate, NAD+, S-adenosyl methionine (SAM) which are co-factors of the basic epigenetic machinery driving epigenetic reprogramming. Mitochondrial metabolites also provide bioenergetics to support cell growth.

**References:**

- DNA methylome and transcriptome alterations and cancer prevention by triterpenoid ursolic acid in UVB-induced skin tumor in mice. *Mol Carcinog.*, 2019
- Tobacco carcinogen 4-[Methyl(nitroso)amino]-1-(3-pyridinyl)-1-butanone (NNK) drives metabolic rewiring and epigenetic reprogramming in A/J mice lung cancer model and prevention with Diallyl Sulphide (DAS). *Carcinogenesis*, 2021
- Pten-knockout regulates metabolic rewiring and epigenetic reprogramming in prostate cancer and chemoprevention by triterpenoid ursolic acid. *FASEB J.*, 2022
- The environmental carcinogen benzo[a]pyrene regulates epigenetic reprogramming and metabolic rewiring in a two-stage mouse skin carcinogenesis model. *Carcinogenesis*, 2023
Professor Kong developed an interest in Pharmacokinetics (PK)-Pharmacodynamics (PD) and PKPD modeling and simulation when he was a PhD student with Professor William J. Jusko; a world renown PKPD scientist, in the 1980s. While in Professor Jusko’s lab, he developed one of the first generation of Indirect Response (IDR) PKPD model “Pharmacokinetics and pharmacodynamic modeling of direct suppression effects of methylprednisolone on serum cortisol and blood histamine in human subjects”. Kong AN, Ludwig EA, Slaughter RL, DiStefano PM, DeMasi J, Middleton E Jr, Jusko WJ. Clin Pharmacol Ther. 1989 Dec;46(6):616-28. Subsequently, Professor Kong has been continuing working on PKPD studies and modeling of the blood concentrations of dietary phytochemicals and their corresponding pharmacodynamic responses/pharmacological effects.

References:
Pharmacokinetics and Pharmacodynamics of the Triterpenoid Ursolic Acid in Regulating the Antioxidant, Anti-inflammatory, and Epigenetic Gene Responses in Rat Leukocytes. Mol Pharm. 2017 Nov 6;14(11):3709-3717.
Pharmacokinetics, Pharmacodynamics, and PKPD Modeling of Curcumin in Regulating Antioxidant and Epigenetic Gene Expression in Healthy Human Volunteers. Mol Pharm. 2019.
Pharmacokinetics and Pharmacodynamics of Anthocyanins after Administration of Tart Cherry Juice to Individuals with Gout. Mol Nutr Food Res. 2023.

Pharmacokinetics and Pharmacodynamics of Anthocyanins after Administration of Tart Cherry Juice to Individuals with Gout.

METHODS AND RESULTS: This study aims to quantitate the major anthocyanins in TC Juice Concentrate (TCJC) and identify the pharmacokinetic (PK) and pharmacodynamic (PD) parameters of the major anthocyanin cyanidin-3-glucosylrutinoside (C3GR). A PK-PD ...
The purpose of this clinical study is to describe the acute pharmacokinetics and pharmacodynamics (PK/PD) of commercially marketed curcumin in normal, healthy human volunteers. COG PK is well-described by a one-compartment model, and the PK/PD model provided reasonable fitting linking the plasma concentration of UA simultaneously with the PD response based on leukocyte mRNA expression. Overall, our results indicate that UA is effective at inducing various phase II DM/antioxidant genes and ...

Development and validation of an LC-MS-MS method for the simultaneous determination of sulforaphane and its metabolites in rat plasma and its application in pharmacokinetic studies.

A validated bioanalytical HPLC method for pharmacokinetic evaluation of 2-deoxyglucose in human plasma.
2-Deoxyglucose (2-DG), an analog of glucose, is widely used to interfere with glycolysis in tumor cells and studied as a therapeutic approach in clinical trials. To evaluate the pharmacokinetics of 2-DG, we describe the development and validation of a sensitive HPLC fluore …

Pharmacokinetics of dietary cancer chemopreventive compound dibenzoylmethane in rats and the impact of nanoemulsion and genetic knockout of Nrf2 on its disposition.
An oil-in-water nanoemulsion containing DBM was formulated to potentially overcome the low F* due to poor water solubility of DBM, with enhanced oral absorption. Finally, to examine the role of Nrf2 on the pharmacokinetics of DBM, since DBM activates the Nrf2-dependent det …

Metabolism, oral bioavailability and pharmacokinetics of chemopreventive kaempferol in rats.

Pharmacokinetics and pharmacodynamics of broccoli sprouts on the suppression of prostate cancer in transgenic adenocarcinoma of mouse prostate (TRAMP) mice: implication of induction of Nrf2, HO-1 and apoptosis and the suppression of Akt-dependent kinase pathway.
PURPOSE: In the present study, we have evaluated the pharmacokinetics and the in vivo prostate chemopreventive activity of broccoli sprouts. ...

Liquid microjunction surface sampling probe electrospray mass spectrometry for detection of drugs and metabolites in thin tissue sections.

Development and validation of an HPLC method for the determination of dibenzoylmethane in rat plasma and its application to the pharmacokinetic study.
The utility of the assay was confirmed by the successful analysis of plasma samples from DBM pharmacokinetics studies in the rats after oral and intravenous administrations....

In vivo pharmacokinetics, activation of MAPK signaling and induction of phase II/III drug metabolizing enzymes/transporters by cancer chemopreventive compound BHA in the mice.
Understanding the molecular basis underlying these diverse biological actions of BHA is thus of great importance. Here we studied the pharmacokinetics, activation of signaling kinases and induction of phase II/III drug metabolizing enzymes/transporter gene expression by BH ...

In vivo pharmacokinetics and regulation of gene expression profiles by isothiocyanate sulforaphane in the rat.


In this study, we used 4967 oligonucleotides microarray to assess the genes that are modulated by SUL in in vivo rat livers, as well as time course of expression of these genes. The pharmacokinetics of R- and S-warfarin were comparable in the absence and presence of losartan (no signif ...

Losartan does not affect the pharmacokinetics and pharmacodynamics of warfarin.


Multiple plasma samples were collected over a 6-day period after both warfarin doses for the measurements of R- and S-warfarin concentrations and prothrombin times. The pharmacokinetics of R- and S-warfarin were comparable in the absence and presence of losartan (no signif ...

Pharmacokinetics of methylprednisolone hemisuccinate and methylprednisolone in chronic liver disease.


However, good availability of MP from MPHS and lack of perturbation of MP pharmacokinetics in CLD patients may provide therapeutic advantages in selection of this glucocorticoid. ...

Disposition of methylprednisolone and its sodium succinate prodrug in vivo and in perfused liver of rats: nonlinear and sequential first-pass elimination.


Pharmacokinetics of methylprednisolone sodium succinate and methylprednisolone in patients undergoing cardiopulmonary bypass.

Kong AN, Jungbluth GL, Pasko MT, Beam TR, Jusko WJ. Pharmacotherapy. 1990;10(1):29-34. PMID: 2179900

The pharmacokinetics of methylprednisolone sodium succinate (MPHS) and methylprednisolone (MP) were determined in six patients undergoing open heart surgery with cardiopulmonary bypass. ...

Pharmacokinetics and pharmacodynamic modeling of direct suppression effects of methylprednisolone on serum cortisol and blood histamine in human subjects.


Simultaneous analysis of methylprednisolone hemisuccinate, cortisol and methylprednisolone by normal-phase high-performance liquid chromatography in human plasma.


Definitions and applications of mean transit and residence times in reference to the two-compartment mammillary plasma clearance model.