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## EDITORIAL

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### Cancer Chemoprevention - How Feasible?

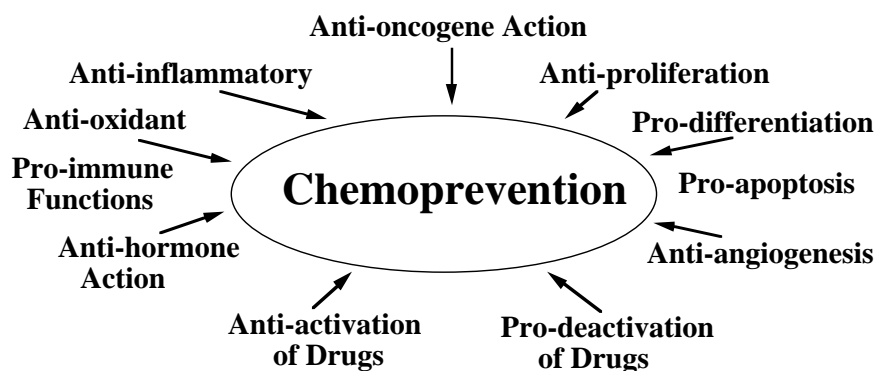
The APJCP routinely includes papers with the focus on chemoprevention and the present issue is no exception. Thus, three papers from India point to the chemopreventive potential of natural materials based on *in vivo* animal modeling (Kumar et al., 2006; Regi Raphael et al., 2006; Sancheti and Goyal, 2006). In addition, Chakraporty et al (2006) and Arif et al (2006) concentrate attention on apoptosis induced by tea components and phthalazines, respectively, while Nishiumi and colleagues document a large scale screening program to assess the ability of indigenous plant materials in Japan to modulate transformation of the aryl hydrocarbon receptor (2006). Furthermore, one of the reports on meetings held in the Asian-Pacific over the last few months also concerns use of natural foodstuffs to prevent neoplasia, bringing seeds under the spotlight (Om, 2006). Clearly there is continuing interest in chemoprevention research at the academic level despite the difficulties that have been experienced with human trials, for example with  $\beta$ -carotene and more recently specific COX-2 inhibitors. The questions we must ask ourselves are when and how all the knowledge that we are researching will find practical application.

As we have documented earlier with reference to publications from International Agency for Research on Cancer (IARC), numbers of compounds which have been shown to be effective in human clinical trials are extremely limited as compared to those shown to have efficacy in animal studies (Tsuda et al., 2004). In Asia there have been very few clinical trials performed (Kakizoe, 2003) but in the United States, agents selected based on preclinical results are now being evaluated in phase I, II and III interventions for various cancers. Development of valid

surrogate end point biomarkers is essential to accelerate progress in this regard and facilitate intervention studies (Greenwald et al., 2002a; 2002b). Given the considerable costs involved with new pharmaceutical development of agents, it is natural that the focus should be on drugs that have already had approval for chronic treatment human ailments, like the aspirin that has stimulated so much investigation of non-steroid anti-inflammatory agents, and natural compounds present in our foodstuffs.

Such natural agents have clear practical advantages with regard to availability, suitability for oral application, regulatory approval and mechanisms of action. Candidate substances such as phytochemicals present in foods and their derivatives have been identified by a combination of epidemiological and experimental studies and plant constituents include vitamin derivatives, phenolic and flavonoid agents, organic sulfur compounds, isothiocyanates, curcumins, fatty acids and d-limonene. Examples of compounds from animals are unsaturated fatty acids and lactoferrin. Recent studies have indicated that mechanisms underlying chemopreventive potential may be combinations of anti-oxidant, anti-inflammatory, immune-enhancing, and anti-hormone effects, with modification of drug-metabolizing enzymes, influence on the cell cycle and cell differentiation, induction of apoptosis and suppression of proliferation and angiogenesis playing roles in the initiation and secondary modification stages of neoplastic development (Liu, 2003; Tsuda et al., 2004) (see the Figure).

Clearly we need to continue exploring mechanisms of action, particularly as they related to surrogate markers that could be employed for intermediate assessment of chemopreventive efficacy. Eventually the attention must



**Figure. Different Mechanisms of Action of Chemopreventive Agents Acting on Initiation/Promotion Stages**

**Table. Projects for an APOCP/UICC Asia Consortium for Chemoprevention**

**Mechanisms Project**

- Determine modes of action of individual agents.
- Assess interactions with other factors
- Identify reliable surrogate markers

**Search Project**

- Screen for potential using biochemical parameters
- Focus on human populations with exceptional nutritional or pharmaceutical characteristics
- Confirm candidate efficacy with single/multi-organ animal models

**Clinical Trial Project**

- Find funding for costs of agents and trial performance
- Identify and set-up recruitment for populations at risk
- Promote marketing of evidence-based health foodstuffs

**Publication Project**

- Stress practical chemoprevention in the APJCP
- Compile, translate and publish books/booklets in Asian languages
- Construct a chemoprevention publication library/website

shift to intervention protocols and these might be best realized in an international context. This is where the APOCP, and possibly also the UICC Asian office which is now under discussion, could play meaningful roles (see the Table).

A number of projects could be envisaged in response to the question posed in the title of the present editorial. The first and most basic is understanding mechanism in a comprehensive fashion to avoid premature clinical trials with

inappropriate target populations (as with smokers and  $\beta$ -carotene). The second is the ongoing search for promising candidates. We have epidemiological as well as toxicological pathology expertise at hand (the efficacy of aspirin was first noted by epidemiologists) and it could well be envisaged that comparison of specific populations exposed to high or low levels of a particular food or constituent might yield new compounds or mixtures warranting further exploration. *In vivo* testing needs to be performed at the whole body level if we are to avoid organ specific negative influence.

Organizing clinical trials in Asia will never be easy but act together we are much more likely to be able to persuade the powers that be, as well as high-risk individuals and the interested general population. The key is knowledge and awareness and we are perhaps not getting the message across in an optimal manner. There is undoubtedly a great deal of interest in health foods - what are we doing as responsible scientists to provide guidance in lay terms that are unequivocal and easy to understand? Persuade the general populace and you persuade the politician - persuade the politician and the funding becomes available. With financial support the infrastructure becomes feasible.

We will naturally continue to stress chemoprevention in the APJCP and rely on your expertise to provide up-to-date reviews and communications of your own research findings. An proposal will be made for those interested in joining an Asian Consortium of scientists for this purpose and we will welcome your input and discussion at the forthcoming APOCP General Assembly and Satellite conferences in Thailand in November of this year.

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