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Editorial

Cancer chemoprevention – An update on a (still) novel and exciting field of oncology

Cancer chemoprevention has come a long way. Wattenberg [1] and Sporn [2] introduced the concept, then there were initial exciting results in the early 1990s, according to which retinoids such as isotretinoin prevent second primary malignancies [3], then tamoxifen was shown to delay breast cancer onset [4], and recently evidence emerged that prostate cancer development can be delayed by finasteride [5]. Two decades or so ago the notion that constituents of fruits and vegetables may prevent cancer was the subject of "fringe" research activities, and results tended to be published in low impact journals. The negative results obtained with β-carotene in lung cancer prevention [6] sharpened our awareness of the notion that robust mechanistic information is paramount to optimise costly and lengthy clinical trials. Today we possess a plethora of mechanistic insights into how dietary constituents such as resveratrol (from red grapes), epigallocatechin gallate (from tea) and curcumin (from turmeric) can interfere with oncogenic events germane to differentiation, death and survival. Many publications on cancer chemoprevention mechanisms now find their way into "heavyweight" journals like J. Biol. Chem., and reviews of this subject occupy high-profile spots in august publications like Nature Reviews Cancer. The current increase in scientific visibility of cancer chemoprevention is, at least in part, the corollary of the high interest by both specialists and lay people in clinical prevention studies, as exemplified by finasteride as a prostate cancer preventive intervention and of dietary fibre intake and the risk of colorectal cancer (*e.g.* [7]).

So the field of cancer chemoprevention is undoubtedly in an exiting phase of development. We hope this special issue reflects this excitement. But – it is a truism to say that – there are several areas of uncertainty associated with this mode of cancer management, and a lot of research still needs to be done. The recent concern over toxicity of some potential chemopreventive agents, and the scepticism by the general public *vis-à-vis* pronouncements by scientists on dietary and lifestyle habits with benefit or detriment to our health show that we still know so little. Also there is considerable head-scratching caused by the emerging picture which suggests that whilst some dietary compounds show cancer chemopreventive efficacy in observational studies, proper clinical trials do not bear this notion out [8]. The overall rationale for this issue is that cogent reviews and succinctly formulated viewpoints often help channel scientific and clinical research energies into areas of special promise, which might motivate clinical and bench scientists to engage in cancer chemoprevention-related activities eventually propelling the field further forward.

In our view there seem to be at least two good reasons for a special EJC issue on cancer chemoprevention: firstly to emphasise the importance of mechanism studies and secondly to initiate a critical rethinking of clinical evaluation paradigms. Several contributions (for example, in this issue, Manson on mechanisms of dietary agents, Izzotti and colleagues on gene/protein changes associated with lung anticarcinogenesis, Collins on antioxidant intervention as a chemoprevention route, Singh and Agarwal on the milk thistle constituent silibinin in skin cancer prevention) illustrate nicely how much we already know, but also how complicated the interpretation of mechanism studies can be in terms of their appropriate application to the clinic. These contributions illustrate impressively the confusing complexity of the scenario and stress the need to delineate primary mechanisms, that may play dominant roles determining efficacy, and to distinguish them from subsidiary ones. The recent demise of selective COX-2 inhibitors as cancer chemopreventive agents, due to unacceptable cardiovascular toxicity brings the message home that we probably also need more toxicity-directed mechanistic evaluation of putative chemopreventive agents (Hull, this issue).

In a fascinitaing account, Veronesi and Bonanni (this issue) trace the recent progress in cancer chemoprevention from bench research to applied clinical oncology. They proffer the pertinent viewpoint that among neoplastic diseases, lung cancer remains arguably the most intractable to preventive intervention. Van Zandwijk

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(this issue) addresses this issue further by exploring in depth the intricacies of lung cancer carcinogenesis germane to its prevention. The finasteride trial has elicited a lot of questions, which when addressed, may improve future prostate cancer prevention trial design (Mellon, this issue). Experience with selective oestrogen receptor modulators seem to bear out the notion that breast cancer – in contrast to lung cancer – may be one of the malignancies amenable to chemoprevention strategies (Decensi, this issue).

An improved understanding of the pharmacokinetics of cancer chemopreventive agents, before they undergo extended clinical testing, is pivotal to improve trial design. For example the low systemic availability, which a lot of phytochemical polyphenols like curcumin (Sharma and colleagues, this issue) suffer from, will influence the choice of tissue type onto which chemopreventive intervention is targeted. We also need a better understanding of the pharmacodynamics of cancer chemopreventive agents. One of the major drawbacks of many past trials has been that there were no markers of efficacy, which would allow an assessment to be made as to the efficacious dose. In this issue, Ranger-Moore and colleagues suggest that karyometry may be a promising tool to assess degree of progression of intraepithelial neoplasia as affected by cancer chemopreventive agents.

One emphasis of this issue is the description of the immense variety of sources of potentially promising cancer chemopreventive agents, whether they are established drugs, dietary agents, whole foodstuffs or chemicals endogenous to the human organism, and the astonishing range of mechanisms which they engage. Many of these sources have only just started to be investigated, and a lot of further preclinical work is required to separate the promising interventions from the less promising ones. The paper by Corpet and Pierre (this issue) suggests that there are animal models that may be extremely useful in helping to perform such separation. Thiery-Vuillemin and colleagues (this issue) discuss the question of whether some of the molecularly targeted cancer chemotherapeutic agents developed in recent years may have potential as cancer chemopreventives. Megdal and colleagues (this issue) have gathered together fascinating evidence to suggest that light deprivation, thus reduced exposure to endogenous melatonin, may increase the risk of breast cancer. Many readers will take comfort from the notion that beer contains a plethora of interesting substances with potentially chemopreventive properties (Gerhäuser, this issue). Afficionados of fruits and berries will be encouraged by the review of Cooke and colleagues (this issue) which suggests that the anthocyan flavonoids not only confer intense red or blue colour on fruits, but may also be anti-carcinogenic. It is important to stress that to avoid conceptual confusion one needs to distinguish between dietary mixtures on the one side and isolated constituents such as curcumin and resveratrol on the other. Whilst the isolated constituents may (or may not) explain the efficacy of the mixtures, they are often investigated at doses or concentrations that far exceed those at which they occur naturally, rendering them novel interventions in their own right with little relationship to the dietary sources from which they emanated. Arguably, the institution that has over the years driven the search for novel chemopreventive interventions most effectively is the Cancer Chemoprevention Branch of the NCI in the USA. In this issue, Crowell allows us a fascinating insight into the discovery and development strategies of the NCI chemoprevention agent development research programme.

We hope that this special issue will appeal to all members of the onocological reesearch community, may they be specialists in cancer chemoprevention or novices to the field. We hope that whilst the former might find in it nuggets of novel information, the latter may value it as an appropriate and enlightening introduction to a most promising field of oncological research endeavour.

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Andreas Gescher
William P. Steward

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