European Science Foundation

Standing Committee for the European Medical Research Councils (EMRC)

ESF EMRC EXPLORATORY WORKSHOP

Development of novel cancer chemopreventive agents in Europe:

Review of preclinical models and early clinical studies and discussion of future collaborative European initiatives

Heidelberg, Germany, 18-20 September 2005

Convened by:

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1. Executive Summary

Development of novel cancer chemopreventive agents in Europe – Neglected Cinderella or Rising Phoenix?*

Agents that prevent cancer, delay its onset, or revert premalignant conditions could have a dramatic beneficial impact on the health of citizens in Europe and elsewhere. Although there is an urgent need for such novel agents preventing malignancies, researchers in the field suspect that this area of scientific endeavor in Europe leads a Cinderella existence, both in terms of perception of importance, research funding and investment.

In order to review current activities in this prevention field and to seek a consensus evaluation, an exploratory workshop was held in September 2005 at the German Cancer Research Center (DKFZ) in Heidelberg, Germany, sponsored mainly by the European Science Foundation (ESF), and also supported by the European Association for Cancer Research (EACR) and the German Cancer Society. The 35 experts from European countries and the United States of America assessed the state-of-the-art of cancer chemoprevention research in Europe. Presentations during the workshop summarized impressive and high quality of work currently conducted in Europe in the area of experimental and clinical cancer chemoprevention research. A considerable array of novel, diet-derived agents discovered in laboratories across Europe awaits further testing in rodents and/or in human trials. However, in contrast to the US, where the NCI fosters and coordinates many chemoprevention research and clinical activities, Europe lacks an appropriate coordinating and supporting infrastructure for such activities. This situation seems to be particularly apparent with respect to large clinical trials, of which the outcome could offer great potential health benefits and lower costs for health care of increasingly aging populations. Therefore also in Europe financial support must be earmarked to enlarge the further

*The major body of this report has been submitted to the *European Journal of Cancer* for publication: Clarissa Gerhauser, Helmut Bartsch, James Crowell, Silvio De Flora, Maurizio D'Incalci, Christian Dittrich, Norbert Frank, Enrico Mihich, Christian Steffen, Giampaolo Tortora, Andreas Gescher, Development of novel cancer chemopreventive agents in Europe – Neglected Cinderella or rising phoenix? A critical commentary*

development of chemopreventive agents, and most importantly their clinical efficacy and safety evaluation. The workshop recommended that participants should persuade key persons in each member state to influence policy making and to boost support for prevention research within EU-framework programs. The urgent need and the rational for developing novel cancer preventive agents and the potential expediency in health political terms derived from their clinical testing, should be propagated and explained to clinicians, practitioners, policy makers and to the society at large. Establishing an organization or institutional focal point for cancer prevention research in Europe would greatly facilitate the continued development of this area, and for instance EORTC should be one of the candidates to be approached. Such action could help to boost the area of chemoprevention agent development and its applications in Europe, shifting emphasis from the cure of end-stage disease to early reversal of carcinogenesis.

2. Scientific content of the event

Agents that prevent cancer, delay its onset, or revert premalignant conditions could have a dramatic beneficial impact on human health. Although there is an urgent need to develop cancer chemopreventive agents, researchers in the field suspect that this area of scientific endeavour in Europe leads a Cinderella existence, both in terms of perception of importance and research funding. In order to review current activities in this prevention field and to seek a consensus position, an exploratory workshop was held in September 2005 at the German Cancer Research Center (DKFZ) in Heidelberg, Germany, sponsored mainly by the European Science Foundation (ESF), and also supported by the European Association for Cancer Research (EACR) and the German Cancer Society (DKG). The 35 experts from European countries and the United States of America assessed the state-of-the-art of cancer chemoprevention research in Europe. The aims that the workshop organizers had pre-defined were i) assessment of the usefulness of animal models for agent identification, ii)

review of ongoing preclinical and clinical work on novel agents, and iii) discussion of potential biomarkers predictive for cancer preventive efficacy. iv) Finally, the potential role that European pharmaceutical industries could play in furthering chemopreventive agent development was to be defined. Overall the workshop aimed at raising the awareness among European clinical and laboratory researchers of the importance of the development of novel, efficacious and safe cancer preventive agents.

2.1. Experimental models of cancer chemoprevention

There are four types of preclinical models used to study mechanisms and efficacy of putative cancer chemopreventive agents: carcinogen-induced rodent models, nude mice bearing transplanted human tumours, genetically modified animals and conditional rodent models. Whereas “classical” chemical-induced models reflect the primary prevention scenario, more recent carcinogenesis models attempt to reproduce clinical conditions that mimic the early phases of tumour development between cellular transformation and the occurrence of small detectable lesions. Experimental models may also establish the extent of parallelism between tumour prevention and modulation of intermediate biomarkers, which can subsequently be validated in clinical trials.

Rodent models are used for the evaluation of mechanism-guided combinations of agents. The nude mouse model harbouring human cancer-derived cells allows hypotheses to be tested resulting from mechanistic experiments in vitro with the same human cell types. As an example, comparative effects of potential prostate cancer chemopreventive agents on levels of prostate-specific antigen (PSA) in both nude mice bearing human prostate tumours and men with prostate cancer permit rapid decisions to be taken as to which agent or food supplement is worthy of further clinical evaluation (1,2). In rodents defective in oncosuppressor genes (p53 or fhit), in which tumours are induced by cigarette smoke and/or UV light, drugs and dietary components have been assayed for their ability to prevent lung

tumourigenesis (3). Genomic, transcriptomic, and proteomic changes in the target organ can be probed for as intermediate biomarkers of efficacy (4). The ApcMin mouse model, which develops intestinal adenomas due to a mutated APC gene, allows deductions to be made as to interactions between cancer development (and its inhibition) and oncogenic defect, mimicking conditions underlying human colon carcinogenesis. A provocative meta-analysis of published results of studies on pro- and anti-carcinogenic agents affecting colorectal carcinogenesis in ApcMin mice, azoxymethane-treated rats and in humans has been conducted (5). This comparison suggests that rodent models approximately predict effects in humans and, although not accurate for all agents, they complement each other, providing suitable tools for the development of novel agents and exploration of mechanisms. Conditional models of carcinogenesis are research tools, in which oncogenes or defective tumour suppressor genes can be switched on and off (6). Suitably transfected mice allow testing of in vivo mechanistic hypotheses germane to cancer chemoprevention. The consensus view emerged that, given robust hypotheses to be tested, all of these models are useful tools for agent development. A particular advantage of these models is the possibility to study chemopreventive effects on tumour development as well as on host-dependent susceptibility factors such as inflammation or angiogenesis.

2.2. Preventive agents under development

Several promising putative chemopreventive agents are currently under preclinical investigation in Europe. These include diet-derived phytochemicals, i.e. flavonoids, terpenes, glucosinolates and synthetic agents such as polyethylene glycol (PEG). The broad–spectrum chemopreventive effects of xanthohumol, isolated from hop, are an instructive paradigm (7,8). Short-term animal models, such as the rat uterotrophy model, have been useful in the exploration of its target organ bioavailability and activity. The rice bran-derived flavone tricin delays intestinal carcinogenesis in ApcMin mice (9). Extra-virgin

olive oil contains several anti-oxidants in relatively high concentrations (10,11), amongst which the lignan oleocanthal was recently identified and shown to be a potent inhibitor of cyclooxygenase enzymes (12). A diet rich in processed tomato products is associated with a reduced risk of prostate cancer in humans (13). Whether the carotenoid lycopene is the only responsible constituent in tomato remains to be demonstrated. Important for the design of preventive trials is the observation that the anti-oxidant activity of lycopene and other carotenoids is characterized by a U-shaped dose-response curve exhibiting pro-oxidant effects at higher concentrations (14). Isothiocyanates and other anticarcinogenic breakdown products of glucosinolates (sulphur-containing glucosides) are obtained from cruciferous vegetables (15). Regular consumption of Brassica vegetables leads to a cancer risk reduction, especially in carriers of a null polymorphism for the detoxifying enzymes glutathione S-transferases T1 and M1 (16). Individuals at increased risk for lung and colorectal cancers may benefit from the protective effects of novel cultivars of broccoli with increased levels of glucosinolates (17). The modulation of gene expression, measured by microarray techniques in the colon epithelium before and after dietary intervention in human and rodents' colon tissue, may help to identify molecular signatures by dietary components and regimens associated with a reduced colon cancer risk (18,19). Polyethylene glycol (PEG) 8000, used as a laxative, may be a promising synthetic agent for the chemoprevention of experimental colorectal cancer (20), and its efficacy in humans should be verified.

Many putative cancer chemopreventive agents inhibit angiogenesis, blocking the supply of pre-neoplastic and neoplastic tissue with blood and thus retard tumour growth. The “angiopreventive” properties and mechanisms of several agents, including N–acetyl–L–cysteine (NAC), the green tea flavonoid epigallocatechin gallate (EGCG), and synthetic retinoids such as 4–hydroxyphenylretinamide, have been determined in both in vitro and in vivo test systems and through gene expression profiling of endothelial cells (21,22).

2.3. Clinical studies

Pharmaceutical and/or dietary chemopreventive interventions can be applied to asymptomatic healthy individuals (primary prevention), subjects with a premalignant condition (secondary prevention) and patients after cancer therapy (tertiary prevention) (23). Phase III clinical trials operate in secondary or tertiary prevention settings. Although the area of clinical cancer chemoprevention trials certainly needs to be strengthened in Europe, there are very interesting clinical activities ongoing in breast cancer chemoprevention. Trials of selective oestrogen receptor modulators (SERMs) like tamoxifen or aromatase inhibitors explore their effect on occurrence or relapse of malignancy in high-risk individuals and in patients (24). Selection of the lowest effective dose of drug to minimize adverse effects is an important issue germane to clinical breast cancer chemoprevention. For instance, studies are addressing the potential to combine hormone replacement therapy or aromatase inhibitors with low doses of anti-estrogens, while higher doses of anti-estrogens are being compared to aromatase inhibitors in women at high risk. The development of preventive agents for hormone receptor-negative breast cancers remains a challenge. Approaches to lung cancer chemoprevention have turned out to be particularly difficult. The outcome of clinical trials such as the CARET and the ATBC-study using ? -carotene or 13-cis-retinoic acid to prevent primary lung tumours or second primary head and neck cancers was negative. Final analyses of the results of these trials emphasized critical issues such as patient selection, mechanistic understanding of the resistance of lung carcinogenesis to retinoids (e.g. involving differential expression and effects of RAR-? isoforms, Ref. 25), and need for recruitment of sufficiently high numbers of study subjects (26). Phase I/II trials, conducted in parallel with preclinical studies in nude mouse models, are used to evaluate phytochemicals and hormone therapy for chemoprevention of prostate cancer. This promising strategy seems particularly suitable for the study of the effect of novel combinations of chemopreventive agents. Such randomized, double-blind, placebo-controlled crossover studies are being conducted in men

with prostate cancer and rising PSA (27). Colorectal chemoprevention trials in patients with polypomatosis depend on the correct selection of the target population to minimize adverse effects and to ensure cost-effectiveness of the intervention (28). In certain circumstances standard colonoscopy and occult blood testing may be more cost-effective than medication with high dose aspirin (325 mg per day), but the benefits of aspirin on other target systems (e.g. heart disease) may provide an additional advantage. Preclinical and early clinical pilot studies can provide mechanism-based pharmacodynamic and pharmacokinetic parameters that should be exploited to optimize the design of subsequent Phase II/III trials (29). For example, curcumin, a putative colorectal cancer preventive agent derived from curry, was tested in a pilot study in patients candidate to colectomy (30). Curcumin levels and pharmacodynamics in the target tissue obtained were measured prior to (biopsies) and post-surgery (surgical specimens) (31).

Three general issues seem to be important for the implementation of successful clinical prevention trials: i) selection of relevant target populations, either healthy volunteers, individuals at higher cancer risk or cancer patients, ii) definition of measurable disease-relevant end-points and agent-related biomarkers to reflect efficacy, and iii) basing trial design on results obtained in biologically relevant preclinical models.

2.4. Biomarkers

The development of novel targeted anticancer strategies necessitates identification of surrogate-biomarkers for the early assessment of drug- or nutritional efficacy. Premalignant lesions in the oral cavity and oropharynx are accessible target lesions for prognosis, which can also be exploited as surrogate-endpoint markers for chemopreventive intervention. Genetic analyses with microsatellite markers of cells (brushed samples) of the oral cavity provide high sensitivity and specificity to detect genetic lesions (32), indicating whether a genetic instability is associated with cancer risk. The clinical evaluation of the EGFR-

tyrosine kinase inhibitor gefitinib as adjuvant intervention in oral leukoplakia, a pre-malignant condition, was planned in France (33). The trial was halted prematurely by health authorities in 2003, because of the interstitial pneumonia reported to occur in gefitinib-treated Japanese cancer patients.

Minimal invasive procedures together with easy accessibility are being further developed for the early diagnosis of cervical carcinoma. In addition to the classic Papanicolaou smear-test, new optical techniques such as optical coherescence tomography and confocal imaging allowing the mapping of subsurface structures are being validated (34,35). Visualization of EGF-receptors with quantum dots conjugated with anti-EGF-receptor antibodies allows detection of changes at the molecular level (36).

For assessing efficacy of breast cancer intervention the validation of biomarkers remains an urgent need (37). It is complicated by a number of issues: Target populations for intervention studies are difficult to identify. Breast tissue is histopathologically very heterogeneous. Proliferation markers cytological atypia, gene expression or gene methylation patterns in cells derived from nipple aspirates, ductal lavage, fine needle or core biopsies have been measured alone or in combination with serum markers and mammographic density (38). To date these markers have not yet been ascertained in terms of their usefulness to assess the efficacy of preventive agents. A trial of celecoxib is currently performed (sponsored by the US-NCI) in order to determine optimal biomarker combinations. Surgical breast tissue sample banks allow extensive analysis by modern technologies that will provide information on the validity of biomarkers. Once the outcome of treatment intervention will be known, such data bases can be evaluated retrospectively. The Danish Cancer Society currently coordinates the collection of clinical data and breast tissue samples integrating genomic, transcriptomic, proteomic and immunohistochemical approaches. Challenging translational research projects, such as this one, which will undoubtedly impact on the field of biomarker determination, merit long-term support (39).

2.5. Role of pharmaceutical industry

Three major reasons explain why the pharmaceutical industry in general has been reluctant to invest in the development of chemopreventive drugs: i) Chemoprevention studies last many years and thus proof of efficacy is unlikely to be established before patent expiry. ii) There is a dearth of validated surrogate end-points to measure protective efficacy, the unequivocal end-point being the reduction in cancer death rate, which requires costly long-term studies. iii) The safety profile of a potential chemopreventive agent needs to be rigorously established, as often subjects who are at increased risk of cancer but otherwise healthy, would need to be treated for a long time. This situation requires a most vigorous proof of lack of long-term toxicity, raising the cost of agent development. iv) Many agents proposed for primary chemoprevention cannot be patented; hence the costs of clinical trials cannot be sustained by the industry (40). As to dietary supplements, such as vitamins and trace elements, solid scientific evidence to buttress their marketing as cancer chemopreventive agents is often lacking. In some cases, the available scientific information that would justify the promotion of vitamin C, E, and selenium supplements as cancer preventive agents has been exaggerated for marketing purposes. Moreover, the indiscriminate intake of supplements can cause unwanted side effects, for instance as reported for selenium, which has lead to cases of acute intoxication (41). Until these issues are resolved, the interest of the pharmaceutical industry in this field is likely to remain low. Nevertheless there are promising possibilities in sight: New cancer therapeutic drugs developed by the pharmaceutical industry, which are devoid of toxic side effects and target selective growth controlling pathways in cells, e.g. cyclin-dependent kinase inhibitors, cell surface receptor antibodies and anti-angiogenic agents, might also be used to prevent progression of precancerous lesions to a malignant tumour (42). An intervention trial with such drugs in oral leukoplakia patients has been initiated (see Section 4). In addition, chemopreventive phytochemicals that boost the host's anti-inflammatory defence could

sensitize malignant cells to cytotoxic agents and thus should be explored for their usefulness as adjuvants during (or even after) treatment with targeted cancer chemotherapeutic agents, possibly allowing the curative drug dose to be lowered.

2.6. Cancer chemoprevention agent development in the USA

In the United States the public health agenda of cancer prevention has been advanced to date primarily by academically based researchers with the support of government programs. This effort is centred in the Division of Cancer Prevention of the National Cancer Institute, and this continued commitment over the last two decades has provided a focal point through which to stimulate this new area of prevention research. Encouragingly, several cancer centres in the USA have now established cancer prevention clinics, the Center for Scientific Review of the National Institutes of Health has chartered a peer review study section for grant applications in the area of cancer chemoprevention and nutritional intervention, several professional scientific organizations have established meetings, symposia, and journals dedicated to cancer prevention, the NCI and the FDA have established a task force to examine regulatory issues pertaining to cancer prevention, and public advocacy groups have incorporated the message of prevention. Thus, public awareness continues to grow that scientific progress in risk assessment, early detection, and interventions will render some cancers akin to other chronic diseases of aging. In addition, it is important that the Division of Cancer Prevention proactively seeks to engage the international research community and private sector pharmaceutical, food, and nutraceutical industries, and advances the field of cancer prevention by supporting preclinical testing, leading to clinical trials of potential cancer preventive agents (43). One mechanism is the Rapid Access to Preventive Intervention Development (RAPID) program, which assists academically based investigators to develop novel, potential cancer preventive agents. Based on the peer review process, applications are accepted for applied drug development using the contract resources of the

Division of Cancer Prevention. For example, product scale-up or preclinical toxicology studies might be supported. The ultimate intention is to bring a potential preventive drug to a clinical test. All data and technical reports become the property of the applicant; the Division of Cancer Prevention assumes no ownership. The program is advertised and supported internationally (www3.cancer.gov/prevention/rapid/index.html).

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3. Assessment of the results, contribution to the future direction of the field, outcome

Cancer research scientists and physicians recognize that the process of carcinogenesis occurs over decades before manifesting itself clinically. The economic and medical burden of cancer can be reduced by preventing, reversing or delaying this process through dietary, nutritional and lifestyle changes, enhanced screening, and immunological and pharmacological interventions. An impressive amount and high quality of work is currently conducted in Europe in the area of experimental and clinical cancer chemoprevention research. A considerable array of novel, diet-derived agents discovered in laboratories across Europe awaits further testing in rodents and/or in human trials. Promising chemopreventive agents were either detected by extensive in vitro screening in a series of complementary test systems, by epidemiological observations or by serendipitous findings. However, in contrast to the US, where the NCI fosters and coordinates many chemoprevention research and clinical activities, Europe lacks an appropriate coordinating and supporting infrastructure for such activities. This situation seems to be particularly apparent with respect to large clinical trials, the outcome of which could offer great potential health benefits and lower costs for health care of increasingly aging populations. Therefore it seems prudent to suggest that more financial support should be earmarked also in Europe to buttress the development of novel chemopreventive agents, and especially their clinical evaluation. EU policy makers should be influenced to boost support for chemoprevention research within EU-framework programs. The urgent need and the rational for developing novel cancer preventive agents and the potential expediency in health

political terms derived from their clinical testing, should be propagated and explained to clinicians, practitioners, policy makers and to the society at large. Establishing an organization or institutional focal point for cancer chemoprevention research in Europe might be a suitable strategy to facilitate the continued development of this area. The EORTC is one candidate. Such action could help to transform the area of chemoprevention agent development in Europe from a neglected Cinderella to a rising phoenix, shifting emphasis from the cure of end-stage disease to early reversal of carcinogenesis.

4. Final Program

Saturday 17 September 2005

Evening — *Arrival*

Sunday 18 September 2005

10:00 — *Opening of the workshop*

Welcome Address: O. D. Wiestler, Scientific Director DKFZ Heidelberg

Presentation of the European Science Foundation (ESF)
Carole Moquin-Pattey (Standing Committee for European Medical Research Councils)

Session 1: Animal models of carcinogenesis - their value in cancer chemopreventive agent development

Chairperson**: Silvio De Flora** (IT); **Andreas Gescher** (UK)

10:30 – 10:50 — **Silvio De Flora** (IT) Models of lung carcinogenesis and cancer chemoprevention

10:50 – 11:10 — **Fritz Schröder** (NL) Models of prostate cancer

11:10 – 11:30 — **Alan R. Clarke** (UK) Conditional models of APC deficiency

11:30 – 11:50 — **Denis Corpet** (FR) Colon carcinogenesis chemoprevention: Min mice and carcinogen-initiated rats, what do they teach us?

11:50 – 12:30 — **Discussion:** Which animal models are most useful in novel agent development?

12:30 – 13:30 — *Lunch*

Session 2: Mechanisms and preclinical activity of promising cancer chemopreventive agents in Europe

Chairperson: **Helmut Bartsch** (DE)

13:30 – 13:50 — **Clarissa Gerhäuser** (DE) Xanthohumol from hops

13:50 – 14:10 — **Andreas Gescher** (UK) Novel flavonoids

14:10 – 14:30 — **Robert Owen** (DE) Polyphenolic antioxidants

14:30 – 14:50 — **Wilhelm Stahl** (DE) Lycopene: Antioxidant and non-antioxidant properties

14:50 – 15:10 — *Coffee break*

15:10 – 15:30 **Ian Johnson** (UK) Glucosinolate breakdown products in colorectal cancer prevention

15:30 – 15:40 **Denis Corpet** (FR) Colon cancer chemoprevention by dietary PEG

15:40 – 16:00 **Adriana Albini** (IT) Anti-angiogenesis in a chemopreventive setting: the rational of ''angioprevention''

Chairperson: **Enrico Mihich** (USA)

16:00 – 16:45 **James A Crowell** (USA) *Special lecture:* Cancer chemopreventive agent development in the US - recent achievements and current activities

16:45 – 18:00 **Discussion** The European dimension: How can we better co-ordinate and optimise cancer chemopreventive agent discovery and development in Europe? Can the NCI help? How could we collaborate?

18:00 *Informal dinner at the DKFZ*

Monday 19 September 2005

Session 3: Clinical pilot studies of cancer chemopreventive agents in Europe - update and future direction

Chairpersons*:* **Giampolo Tortora** (IT); **Christian Dittrich** (AT)

a. Breast cancer

09:00 – 09:40 **Andrea Decensi** (IT) Current status of trials loking at SERMS and aromatase inhibitors

b. Lung cancer

09:40 – 10:00 **Nico van Zandwijk** (NL) Chemoprevention of lung cancer

c. Prostate cancer

10:00 – 10:20 **Fritz Schröder** (NL) Past and current clinical studies of prostate cancer in nude mouse models (new drugs, preventive agents)

10:20 – 10:40 *Coffee break*

d. Colorectal cancer

10:40 – 11:00 **Ole Kronborg** (DK) Colorectal cancer: What can we learn from past and current clinical studies of NSAIDs and COX-2 inhibitors?

11:00 – 11:20 **William P Steward** (UK) Early clinical trials with polyphenols

11:20 – 12:30 **Discussion** Promise and limitations of current clinical studies – where do we go from here?

12:30 – 13:30 *Lunch*

Chairpersons**:** **Julio E.Celis** (DK); **Christian Steffen** (DE)

e. Oral leukoplakia

13:30 – 13:50 **Jean-Charles Soria** (FR) Gefitinib as a chemopreventive agent in oral leukoplakia: a postmorten analysis

13:50 – 14:10 **Jon Sudbø** (NO) Prevention – Therapy convergence and the oral IEN model

14:10 – 14:30 **Rudy Brakenhoff** (NL) Precursor lesions in the oral cavity and oropharynx: ideal target lesions for chemoprevention

f. Biomarkers

14:30 – 14:50 **Boudewijn J.M.Braakhuis** (NL) Biomarkers of risk in patients with oral premalignant lesions

14:50 – 15:10 **Anne Thérèse Vlastos** (CH) Use of biomarkers as surrogate endpoints to assess the efficacy of intervention (cervical cancer)

15:10 – 15:30 *Coffee Break*

15:30 – 15:50 **Anthony Howell** (UK) Biomarkers to assess efficacy of breast cancer interventions

15:50 – 16:10 **Julio E.Celis** (DK) Integrating proteomic technologies in breast cancer prevention research

16:10 – 16:30 **Joost van Delft** (NL) Vegetable-induced gene expression changes in anticarcinogenic pathways in human and mouse colon

16:30 – 18:00 **Discussion:** Promise and limitations of current clinical studies – How realistic is the use of biomarkers to assess study outcome?

19:30 *Congress Dinner (Old town, Heidelberg)*

Tuesday 20 September 2005

Session 4: Views of the pharmaceutical and nutraceutical industry and ongoing European initiatives

Chairpersons: **Maurizio D'Incali** (IT); **Sally Burtles** (UK)

08:30 – 08:50 **George Blackledge** (UK) Role of pharmaceutical industry in cancer chemopreventive agent development

08:50 – 09:10 **Christian Steffen** (DE) Cancer prevention studies: What can we learn from supplements?

09:10 – 09:30 **Olaf Kelm** (BE) EU Program priorities for cancer: from FP6 to FP7

09:30 – 10:30 **Reports of rapporteurs**

10:30 – 11:45 **Final Discussion** The European dimension: How can we improve clinical cancer chemopreventive agent development in Europe?

11:45 *Closing of the Workshop, lunch and departure*

12:00 **Press conference (only selectd participants)**

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6. Statistical information

Gender:	female	6
	male	27
Age bracket:	34 to >70	
Countries of Origin:	European	10
	USA	
List of countries and participants per country:	Germany	7
	UK	7
	Italy	5
	The Netherlands	5
	France	3
	Denmark	2
	USA	2
	Norway	1
	Austria	1
	Belgium (EU)	1
	Switzerland	1