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CURRENT SCIENTIFIC INITIATIVES

IARC scientific Sections, except the Section of Cancer Information (CIN) and the Section of Environment and Radiation (ENV) which will undergo a separate Review by a dedicated Review Panel in 2012, have been requested to make a presentation on their current scientific initiatives.

Sections have been asked to present one or two areas where the input of the Scientific Council would be valuable. You will find them as follows:

Section of Mechanisms of Carcinogenesis (MCA) – Section Head, Dr Zdenko Herceg
(as of 16 December 2011)

The broad, long-term goal of the Mechanisms of Carcinogenesis Section (MCA) is to advance understanding of mechanisms of carcinogenesis and to contribute to cancer prevention. This is achieved through investigating interactions between the genes, the epigenome and the environment. In collaboration with epidemiology groups, MCA also contributes to the development of translational studies through the discovery and validation of biomarkers of tumorigenesis and environmental exposures. The Section aims to promote the development of cancer research relevant, although not exclusive to, low- and medium-resource countries. Another MCA focus is the development of genetic/epigenetic methods that are applicable to biobanks associated with case-control and population-based studies.

The Section comprises two Groups: the Molecular Mechanisms and Biomarker Group (MMB), and the Epigenetics Group (EGE), both of which work in close collaboration to create synergies and better exploit and further expand unique research tools and expertise. Given the recent changes in MCA and the Molecular Carcinogenesis Group (MOC) due to the departure of the Section/Group head, Dr Pierre Hainaut, announced for December 2011, this moment represents a particularly opportune time to evaluate current priorities and identify new opportunities. Based on recent developments and the emergence of new powerful research technologies it is estimated that the next few years will be fundamental for identifying critical molecular (genomic and epigenomic) changes and genes associated with disease as well as environmental exposures. The primary emphasis of MCA research will be on (although not limited to) the following projects:

1) *Early molecular ("driver") changes in cancer development and their links with environmental exposures*

Although epidemiological studies support the role of the environment in a wide range of human cancers, the precise mechanisms by which environmental exposures promote cancer development and progression remain poorly understood. It is believed that environmental factors promote the development of malignancies by eliciting genetic and epigenetic changes; however, it is only with recent advances in genomics and epigenomics that target genes and the mechanisms underlying environmental influences are beginning to be elucidated. Somatic mutations and epigenetic changes can be "read" as fingerprints of mechanisms of mutagenesis, providing clues on cancer phenotype and gene-environment interactions involved in cancer causation. Previous studies extensively investigated genetic and epigenetic changes in tumours, but current sequencing efforts are challenged with trying to identify genetic/epigenetic events that precede and promote tumour development and to differentiate between passenger and driver events.

Many large-scale sequencing studies will reveal new genes and pathways that are frequently disrupted in specific human malignancies, therefore further studies are needed to identify important early events in carcinogenesis.

One of the priorities of the MMB Group is now to identify mutations and other molecular events that drive the process of tumour initiation and progression and distinguish these events from changes that are merely non-functional passenger events accompanying the transformation

process. These studies are expected to facilitate the identification of environmental exposures associated with these changes. They should also contribute to the discovery and validation of new cancer biomarkers. Information gained from these studies should provide the basis for the development of a strong translational cancer prevention and control programme on specific human cancers, with the emphasis on cancers associated with low-resource countries. Finally, MMB is expected to use its position as the IARC hub for mechanistic studies to foster international collaboration and to make significant contributions to molecular epidemiology.

2) Epigenetic deregulation induced by early life exposure and cancer risk

Changes in the epigenome may be at the heart of intra-uterine programming of childhood and adult diseases, including cancer. Adaptive responses during early life may include changes in different developmental pathways (such as production and expansion of somatic stem/progenitor cells, metabolic changes, production of and sensitivity to hormones), a combination of which may alter normal development of tissues and organs. These changes may constitute the basis for differential responses to environmental stressors and susceptibility to cancer. The potential mechanisms by which early life exposure may fix and propagate deregulated gene activity states and altered long-term risk of cancer include DNA methylation and non-coding RNAs.

The EGE Group is leading a multidisciplinary study to investigate whether early life events (environmental exposure) influence epigenetic reprogramming during embryonic development and if that epigenetic deregulation contributes to the etiology of cancer risk in childhood and adulthood. This study will take advantage of large mother-child cohorts (with high quality, detailed information on environmental/dietary/lifestyle factors and collection of biological samples) for which the recruitment has been completed (including I4C consortium). These unique cohorts will be combined with powerful tools for epigenomic analysis of large series of biological samples and next generation sequencing (including IARC's NGS platform). Demands for faster, cheaper and less labour-intensive technologies are increasingly being met by several emerging technologies that have a demonstrated capacity to deliver next-generation solutions for fast and affordable sequencing in epigenome-wide and high-throughput settings. With the establishment of the next generation sequencing platform at IARC, as well as other high-throughput platforms, we will take advantage of this facility, which is likely to play an important role in epigenetic research as well as in other molecular epidemiology studies.

Questions for the Scientific Council (MCA)

Most previous studies of genetic/epigenetic changes associated with environmental exposures have been retrospective in nature and considered these changes only after the onset of cancer. A major advance would be the prospective analysis of samples taken prior to tumour development. Application of deep sequencing and the completion of the Cancer Genome Project will lead to the comprehensive discovery of all major changes in the cancer genome/epigenome.

It remains unknown whether genetic/epigenetic changes (candidate genes, mutation and methylation spectra) identified through these initiatives are early or late events. Important questions for our strategy are:

(i) Can we develop models and approaches to discriminate between “driver” and “passenger” events;

(ii) What criteria should we apply to define a set of priority exposures to be addressed in a systematic way;

(iii) How should recent conceptual and technological advances be exploited for studying the causes of cancers relevant to low-resource settings;

(iv) Can we detect exposure-associated and cancer-associated epigenetic changes in surrogate tissues (cord blood, peripheral blood, circulating nucleic acids) as biomarkers; and

(v) Should we consider studies allowing the measurement of molecular events associated with early-life exposure repeatedly over time.

Section of Molecular Pathology (MPA) – Section Head, Dr Hiroko Ohgaki

Molecular pathology of brain tumours

Research in the Section of Molecular Pathology (MPA) focuses on the elucidation of the molecular basis and genetic pathways involved in human neoplasms. Our objectives are to correlate histologically recognized phenotypes with genotypes, to improve the diagnosis and classification of tumours, to identify reliable molecular markers predictive of malignant progression, and to identify clues as to tumour etiology. Currently, our main interest is the molecular pathology of brain tumours. The MPA research programme is a key element in IARC’s work on the elucidation of the mechanisms of carcinogenesis.

1) Molecular bases of congenital diffuse gliomas

Diffuse gliomas detected at birth (congenital glioma) are extremely rare. According to data on 23 000 brain tumours from the French Brain Tumour Consortium, only 20 cases (0.1% of all cases) were listed as low-grade or high-grade astrocytic or oligodendroglial diffuse gliomas (WHO grades II–IV) diagnosed at birth or in very young children (age < 2 years). The very early onset of these tumours suggests the possible involvement of a particular genetic profile or environmental factors (viral infection, chemical exposures, etc.). The identification of such factors may also contribute to our understanding of the etiology of diffuse gliomas arising in adults. We have formed an international consortium to collect frozen samples and paraffin sections of congenital diffuse gliomas. In collaboration with scientists at the German Cancer Research Center, we plan to carry out next-generation sequencing/RNA sequencing for selected cases for which frozen samples are available (approx. 10). If we identify rare germline mutations, novel viral sequences, or typical mutation patterns suggestive of specific exposures, we will validate our results in a large number of cases for which paraffin sections are available.

2) Identification of prognostic biomarkers to predict rapid progression from low-grade astrocytoma to glioblastoma

Low-grade diffuse astrocytoma tends to progress to more malignant histological types, i.e. anaplastic astrocytoma and secondary glioblastoma. However, the period of time until progression significantly varies among patients, and little is known about genetic alterations associated with rapid progression. We plan to make an international collection of samples of diffuse astrocytoma and glioblastoma from the same patients. One group of patients (Group A; 20 cases) will comprise those who progressed from astrocytoma to glioblastoma very rapidly (within 1 year), and another group (Group B; 20 cases) will comprise those who progressed slowly (> 5 years) from astrocytoma to glioblastoma. We plan to carry out next-generation sequencing. Data for astrocytoma and glioblastoma from the same patients will be compared to identify genetic alterations associated with the glioblastoma phenotype. Data will be also compared between astrocytoma Groups A and B, and between glioblastoma Groups A and B. This may lead to the identification of genetic profiles for astrocytomas that are likely to progress rapidly to glioblastomas, which would have a significant clinical impact on the management of patients with low-grade diffuse astrocytoma.

3) Population-based study on genetics and epidemiology of gliomas

We previously carried out a population-based study of glioma in the Canton of Zurich, combining epidemiology, treatment, and genetics for the first time. This study has been commended by neuro-oncology and neuro-epidemiology societies. We included approximately 1000 gliomas diagnosed in 1980–1994 (these glioblastoma patients were treated with surgery and radiotherapy, but not chemotherapy) in this study. Since the early 2000s, most glioblastoma patients have been considered to be treated with the chemotherapeutic alkylating agent temozolomide (TMZ), in addition to surgery and radiotherapy, but it is not known what fraction of patients is actually treated as recommended at a population level.

We are currently carrying out a new retrospective population-based study on glioblastoma patients diagnosed between 2005–2009 in the Canton of Zurich, with the aim of assessing to what extent the currently recommended chemotherapy with TMZ is implemented, and whether chemotherapy significantly improved survival of glioblastoma patients, particularly elderly patients, at a population level. We also plan to carry out a prospective population-based study on glioblastoma patients diagnosed between 2012 and 2015 in the Cantons of Zurich, Basel and Ticino, Switzerland. We plan to collect frozen samples of glioblastoma collected at a population level and to carry out next-generation sequencing. The population-level collection of samples has the advantage of avoiding unbiased sample collection; in clinical trials, elderly patients who have poor clinical performance scores are usually not included.

Questions for the Scientific Council (MPA)

Etiology of brain tumours is largely unknown. The only environmental factor unequivocally associated with an increased risk of brain tumours, including gliomas, is therapeutic X-irradiation. In particular, children treated with X-irradiation for acute lymphoblastic leukaemia show a significantly elevated risk of developing gliomas and primitive neuroectodermal tumour, often within 10 years after therapy. We plan to carry out next generation sequencing using

tumours in which sufficient clinical and exposure data are available, to assess whether there are specific genetic alterations associated with X-irradiation and whether these occur in specific genes or sequences. The Scientific Council is asked to consider what methods are best suited to this goal (exomic sequencing, RNA sequencing).

Section of Infections (INF) – Section Head, Dr Silvia Franceschi

Role of human papillomavirus infection and other co-factors in the etiology of cancer and precancerous lesions of head and neck in Europe and India

Head and neck cancer (HNC) is the sixth most common malignancy reported (approximately 550 000 incident cases and 300 000 deaths per year). The Indian sub-continent has the highest HNC incidence in the world, and it accounts for one-third of the world burden. France shows the highest world incidence rates for cancer of the pharynx (nasopharynx excluded). The vast majority of HNC is currently attributed to smoking and chewing tobacco and alcohol drinking. Over the last decade, markers of HPV infection, mainly that of HPV16, have been detected in variable fractions of HNC, with the highest prevalence in cancer of the oropharynx and tonsil. Whilst HPV markers were detected in ~60% of tonsil carcinomas in North America and some European countries, corresponding proportions elsewhere were in the 5–to–20% range. Steady increases in HPV-associated HNC have been reported in the USA and Northern European countries in the last decades but little is known about the corresponding trends in the other world regions.

Differences in the fraction of cancers attributable to HPV from one population to another may derive from differences in the relative importance of different anatomical sites, methodological differences between studies but also from large variations in the burden of HNC still due to tobacco/alcohol use.

Of note, epidemiological and mechanistic evidence, mainly from North America, suggest that HPV-associated carcinomas of the oropharynx/tonsil represent an entity distinct from carcinomas caused by tobacco and alcohol in the oropharynx/tonsil and elsewhere in the head and neck.

The HPV-AHEAD Study was started by the Infections and Cancer Biology Group (ICB) in collaboration with other groups inside and outside IARC. It aims to compare the epidemiological features and the etiology of HNC in Europe and India, with a focus on the role of HPV. Approximately 4000–6000 HNC specimens will be collected from rural or urban areas in India and 6000 from Europe. The specimens will include cancers of the hypopharynx, oropharynx, oral cavity and larynx. Epidemiological and clinical information will also be collected. Cutting-edge laboratory analyses, including HPV genotyping, detection of HPV RNA, histochemical staining, microRNA array, will be applied to HPV-positive specimens.

In addition to uncertainties of the fraction of HNC attributable to HPV in different populations, enormous knowledge gaps exist, however, in respect to the natural history of HPV in the oropharynx/tonsil, including infection frequency, transmission mode, and the very existence of detectable precancerous lesions. In order to elucidate this issue the Infections and Cancer Epidemiology Group (ICE) has started, in collaboration with ICB and research groups in France, the “Study of human papillomavirus and precancerous lesions in the tonsil (SPLIT)”.

SPLIT focuses on the prevalence of HPV infection and precancerous lesions in the tumour-free tonsils of children and adults and in high-risk individuals, namely those shown to have cytological or histological abnormalities, HPV-positivity and/or heavy exposure to tobacco. To provide extra-information, severe dysplastic areas adjacent to tonsil carcinomas will also be included. As in the HPV-AHEAD study, several biomarkers of HPV transcriptional activity and DNA integration status (including p16, *in situ* hybridization, and HPV E6/E7 mRNA) will be assessed in HPV-positive patients.

The new IARC-led studies on HNC have the potential to be a breakthrough in understanding the epidemiology of HNC in different populations and to elucidate the molecular, cytological, and histological changes that accompany the onset of HPV-related and -unrelated HNC.

Questions for the Scientific Council (INF)

(i) What is the fraction of HNC and precancerous lesions truly attributable to HPV in different populations?

(ii) Are there differences between HPV-related HNC and precancerous lesions and those caused by other risk factors, notably smoking?

(iii) What is the scope for decreasing HNC incidence and mortality using prevention strategies (HPV vaccination of adolescents of both sexes) and new treatment approaches that are becoming available specifically for HPV-associated carcinomas?

Section of Nutrition and Metabolism (NME) – Section Head, Dr Isabelle Romieu

Molecular subtypes of premenopausal breast cancer in Latin America: A multicenter population based case-control study – The PRECAMA study

Breast cancer (BC) is the leading cause of cancer mortality among Latin American women, with a large number of incident BC cases among premenopausal women, a major concern since BC in premenopausal women are more likely to be aggressive and have poor responses to therapy. Breast cancer is a heterogeneous disease and presence or absence of Estrogen receptor (ER) and/or Progesterone receptor (PR) expression in breast tumors – a central factor to their clinical behavior and response to treatment modalities – may differ according to risk factors and to molecular pathological characteristics. Recently, a set of five biomarkers (ER, PR, HER2, Epidermal Growth Factor Receptor (EGFR) and Cytokeratins (CK) 5 and 6) have been shown to discriminate basal-like phenotype, thus identifying a group of tumors with particularly poor prognosis. Moreover, mutation of the tumour suppressor gene *TP53* is a strong predictor of poor prognosis, especially among ER+ tumours, independently of the phenotypes described above. There is a lack of specific knowledge on tumour molecular and pathological characteristics of BC in premenopausal women in Latin American countries, where the hormone-dependence status is poorly documented. Knowledge of tumour characteristic is essential in order to identify specific risk factors. While change in reproductive and breastfeeding pattern may play a role, change in diet, obesity and low physical activity and other environmental factors may be likely to be important, as well as the observed decreasing trend of age at menarche.

The PRECAMA project (developed by the Nutritional Epidemiology Group (NEP) with internal collaboration with the Dietary Exposure Assessment Group (DEX) and the Biomarkers Group (BMA) within NME and MCA) is a multicenter population-based case-control study including five Latin American countries (Mexico, Costa Rica, Colombia, Brazil, and Chile). External collaboration between IARC, the Research Institution of these countries and the Fred Hutchinson Cancer Research Center has been established. The major aim of the PRECAMA project is to advance the prevention and management of BC in low- and middle-income countries of Latin America through a better understanding of their molecular, pathological subtypes and the identification of specific endogenous (genetics and genomics) and exogenous factors (biological modifications, behavioral, dietary and cultural factors) and disentangle the interplay of these different factors with regard to breast tumour subtypes and other characteristics. We plan to enroll 2500 cases and controls. Blood and urine samples will be collected for analysis of hormonal and metabolic markers (BMA) and metabolomics (MBA). Tumour samples will be collected in a standardized manner for immunostaining analyses (FHCRC) and extraction of tumour DNA for genetic and epigenetic determination (IARC/MCA). We expect to determine specific molecular and pathological characteristics of premenopausal BC and in the future, identify candidate metabonomics profiles associated with BC risk factors, which may help to identify new metabolic markers that favour the incidence of BC. We are currently in the pilot phase of the project in order to test and standardize procedures.

This new IARC-led project has the potential to improve our understanding of the aggressivity of some premenopausal breast cancer, identify susceptible subgroups and identify modifiable risk factors. Through these activities the PRECAMA project will also provide advanced training, induce a structuring effect on the BC research community in Latin America and influence the public health agenda regarding the management of BC. We plan to extend this project to other parts of the world where premenopausal BC is also increasing to enrich the variability in genetic background and lifestyle and cultural factors.

Questions for the Scientific Council (NME) – Part 1

(i) Is research on premenopausal breast cancer tumour characteristics and risk factors considered a research priority by the Scientific Council?

(ii) Which standardization method for tumour bloc preparation and standardization of analysis would you recommend?

(iii) Is there some specific information or tests we should include in the study?

(iv) Is there a specific hypothesis we should address?

(v) Are you aware of funding sources we could approach to support this project?

Exploring the human metabolome to identify new biomarkers of exposure to cancer risk factors

Assigning risk of a specific cancer to a particular dietary pattern, food or food component is challenging for a number of reasons. These notably include the difficulty of accurately measuring dietary intakes through traditional questionnaires in epidemiological studies, the lack of sufficiently detailed information from food composition tables for specific components, or the existence of hidden dietary sources. These limitations have resulted in attempts to use biomarkers in studies on diet and cancers.

Foods contain a huge diversity of components and contaminants that, once ingested, are absorbed and found in blood, urine and other tissues. Some of these compounds have been used to estimate food consumption or exposure to nutrients/contaminants in population studies. However the number of compounds that have been considered so far in these studies is very limited when compared to the over 20 000 compounds and thousands of contaminants that have been described in various foods. Altogether these compounds form the 'food metabolome'.

Metabolomics constitutes a novel and promising approach to identify in the food metabolome novel biomarkers for food/nutrient intake, as suggested by a few proof-of-concept studies recently published. In the European FP7 NutriTech project we develop innovative metabolomics approaches to address this question on a broader basis. In a top-down approach, sets of plasma or urine samples from the EPIC study (a European cohort study showing considerable heterogeneity in dietary patterns) and from small intervention studies with various foods, are analysed by high-resolution mass spectrometry. Metabolic profiles of high and low consumers of the food/nutrient of interest are compared to identify features characteristic of the high consumers. In a bottom-up approach, data from the scientific literature and from various databases are systematically analysed and compiled in a food metabolome database to identify some of the most promising biomarkers and to aid in the identification of unknown discriminating features unravelled by metabolomics in the top-down approach. This food metabolome database contains data on chemical structures, analytical methods, spectral characteristics, occurrence in foods, metabolism in humans, and previous use as biomarkers if any.

In a second step, targeted metabolomics methods are developed to quantify by mass spectrometry tens of these novel biomarkers and study correlations with dietary intake and cancer outcomes in metabolome-wide association studies (MWAS).

The new biomarkers expected to be discovered in this project should provide more objective measures for dietary assessment that will complement those obtained with classical methods currently used. The characterization and quantification of the food metabolome offers exciting new opportunities to assess exposure to food, nutrients and contaminants with an unprecedented level of detail and accuracy. This should contribute to unravel new associations between dietary factors and cancer outcomes which we have been so far unable to detect.

Questions for the Scientific Council (NME) – Part 2

(i) Do you approve the general strategy proposed for discovery of new biomarkers of exposure?

(ii) What would be your suggestions in terms of biomarkers of exposure most needed for future epidemiological studies?

(iii) What would be your suggestions for other innovative approaches for discovery of new biomarkers of exposure?

Section of Genetics (GEN) – Section Head, Dr Paul Brennan

As part of the evaluation of the Section of Genetics (GEN) in November 2010, short and medium-term objectives of the Section have been recently outlined. Major developments within GEN in 2011 include the development of next generation sequencing and related Genetic Cancer Susceptibility (GCS)-led projects, and these are being covered by other discussions within the Scientific Council (see documents SC/48/6 and SC/48/8). The focus of this GEN presentation will therefore be on Genetic Epidemiology (GEP)-led projects, especially those on kidney and tobacco related cancers. These include two large NIH grants that have been awarded within 2011, the additional opportunities that they present (where the advice of the Scientific Council is specifically requested), and also ongoing GEP initiatives regarding development of specific biorepositories related to tobacco related cancers.

Update on kidney cancer (CAGEKID and genome-wide studies)

CAGEKID is an FP7 funded project (total of 10.5 million €) with the primary goal of identifying 500 renal cancer cases that fulfil all ICGC criteria and subsequently conducting whole genome or whole exome sequencing on tumour and germline (blood) DNA to characterize the whole spectrum of genetic alterations. CAGEKID also includes a transcriptomic component, which will compare RNA in tumour and in non-tumour renal tissue using the RNAseq technology. While the Principal Investigator (PI) of the project is Mark Lathrop at the CEPH, GEP is responsible for identifying all cases to undergo whole genome/exome sequencing as well as development of a broader biorepository of up to 2000 cases with complete biological material and clinical follow-up. As of October 2011, 120 cases had fulfilled all criteria and 50 have undergone whole genome sequencing of both tumour and germline DNA, the rest being prioritized for whole exome sequencing. The broader biorepository within GEP, including cases with at least tumour tissue, germline DNA, and follow-up, currently comprises 1300 cases, with 400 recruited within the last 12 months.

An initial genome-wide association study of renal cancer, comprising 3800 cases and 8500 controls, was published in early 2011 (Purdue *et al.*, Nature Gen 2011). This study, which was led jointly by IARC and US NCI scientists, identified three susceptibility loci including loci that contain the genes *EPAS1* and *SCARB1*, as well as a non-genic region, and that are suggestive of new pathways in renal cancer etiology. The next phase of this GEN project will focus on (i) doubling the sample size to approximately 8000 cases and many more controls; (ii) identifying complete information on clinical outcome; (iii) performing genome-wide analysis of up to 5 000 000 variants including rare genetic variation; and (iv) incorporating an analysis of

RNA expression. An R01 grant application comprising these goals was submitted to the US NCI by GEP scientists (PI: Dr Scelo) during the 2011 financial year, and funding of US$ 4 033 616 was awarded. As part of this award, prospectively collected blood samples from approximately 4000 renal cases will become available from multiple cohorts, and a corresponding number of controls.

Update on lung cancer (TRICL and lung cancer cohort consortium)

Subsequent to the three susceptibility loci for lung cancer reported in 2008 by GEP scientists (Hung *et al.*, Nature 2008; McKay *et al.*, Nat Gen 2008), and other groups, additional genome-wide lung cancer studies have been completed although no additional susceptibility loci have been identified. A US NCI funded initiative to bring together all lung cancer studies (TRICL) was launched in 2010, and GEP scientists have led the meta-analysis of 16 lung cancer GWA studies comprising data on 14 984 cases and 29 665 controls. Initial results indicate that at least one additional susceptibility locus has been identified that is specific for squamous cell lung cancer histology.

Following the GEP-led study in 2010 that showed strong associations for several B-vitamins and related markers and subsequent lung cancer risk as measured in prospectively collected serum from 2700 cases and controls within the EPIC study (Johansson *et al.*, JAMA 2010), we proposed to conduct a much expanded study within the NCI cohort consortium. Twenty-two separate cohorts agreed to take part and an R01 grant to the US NCI was awarded in June 2011 (amount: US$ 5 039 028). This will allow the formation of a lung cancer cohort consortium including approximately 5000 lung cancer cases and a similar number of controls, about one third of which are never smokers and an additional one third are former smokers.

Finally, at the recent NCI cohort consortium meeting (October 2011), GEP scientists presented preliminary results showing strong associations between HPV antibodies and head and neck cancers (particularly for the oropharynx) within the EPIC cohort that were present up to 15 years before diagnosis, and were almost completely absent in a control group of 1500 subjects. A third large cohort consortium focused on head and neck cancers has therefore been proposed to further investigate this, and additional funding will be sought.

Expanding GEN biorepositories

GEP continues to invest in collecting large series of cases (and comparable controls) with extensive biological material (typically blood, snap frozen tumour and non-tumour tissue), histological confirmation and clinical outcome information. The choice of what clinical series to focus on reflects strategic decisions based on several factors, and will drive the scientific questions that GEP scientists will work on in the medium-term. As well as the renal cancer biorepository highlighted above, additional active recruitment is being conducted for the following cancer sites with the aim of recruiting at least 2000 cases for each of: (i) early stage (I/II/IIIA) non small cell lung carcinoma in central and eastern Europe; (ii) head and neck cancers in Brazil and Argentina, with a particular focus on oropharynx cancer; and (iii) nasopharynx cancer in South East Asia. Initial exome sequencing studies in collaboration with GCS of tumour and germline DNA are being planned on these biorepositories including an analysis of up to 50 oropharyngeal tumours, with an additional 50 being analysed at the Brazilian National Cancer Institute, and 50 lung cancers, with a focus on rare tumour types.

Questions for the Scientific Council (GEN)

We are bringing together large cohort consortia for both renal and lung cancers, and plan a similar cohort consortium initiative for head and neck cancers. The primary emphasis of these projects is on (i) genome wide studies; (ii) one-carbon biomarkers; and (iii) HPV infection, respectively. Establishment of these consortia involves a major expense (largely paid for by the US NCI) although offers considerable additional opportunities.

Given the prospective nature of these large series, a major question for us is whether we should consider, in addition to our main hypotheses, trying to develop pre-diagnostic signatures for these cancers, based on serology, plasma or protein based biomarkers. For example:

(i) Are there sensitive methods for measuring circulating tumour DNA that are ready for broader evaluation;

(ii) Are there promising metabonomics or proteomics techniques that we should consider testing on subgroups of these cases (e.g. those diagnoses shortly after provided a blood sample, or even in separate case series); and

(iii) Should we consider additional markers of subsequent cancer risk including telomerase regeneration or markers of inflammation.

Such studies may also require collection of tumour tissue within the cohorts, and the relative priority to place on this is unclear, especially when one can focus on collection of better annotated samples from prospective case series.

Early Detection and Prevention (EDP) – Section Head, Dr R. Sankaranarayanan

Evaluation of the potential impact of helicobacter pylori eradication to prevent stomach cancer: where do we stand?

Despite declining trends in stomach cancer in some areas, this malignancy affects almost 1 million people per year with nearly 700 000 deaths, particularly in developing countries. The main etiologic agent for stomach cancer is Helicobacter pylori, an infection usually acquired in childhood that can lead to preneoplastic lesions and cancer in a fraction of affected subjects. Treatment of H. pylori infections to prevent stomach cancer is a logical consequence of our etiological knowledge, and several antibiotic treatments have shown to be highly efficacious to eradicate infection. However, there is still limited information on the advantages and potential disadvantages of such a strategy, and screening for H. Pylori and treatment of infected subjects is not standard practice in high incidence areas. Some studies have shown improvement of certain preneoplastic lesions of the stomach after eradication, and some small studies have shown reductions in stomach cancer incidence, but there is a need to properly assess the potential impact of eradication on prevention of stomach cancer, the target groups that could benefit, the additional effect on reduction of peptic ulcer disease and other dyspeptic symptoms, as well as the potentially deleterious effects and associated costs of such an intervention, which is not free of controversy. It has been proposed that H. pylori could have beneficial effects on the human body, and that eradication could increase rates of asthma, obesity and adenocarcinoma of the oesophagus, in addition to the potential for development of antibiotic resistance in the context of population based interventions. Considering the enormous health

burden of this disease, it is our responsibility to conduct the necessary research to decide if such an intervention is warranted as a valid public health strategy. We propose to conduct a large, multicentric randomized clinical trial of H. Pylori eradication in high risk areas. Age-stratified samples of individuals or clusters would be randomized to no screening or to screening and treatment of H. pylori positive subjects with standard antibiotic treatment, taking into account information on local antibiotic resistance. The specific outcomes and follow-up intervals are under discussion and could go from passive surveillance through tumour registries to active surveillance of surrogate outcomes of disease, in addition to assessment of other relevant health outcomes potentially associated with treatment or H. pylori eradication itself.

Questions for the Scientific Council (EDP) – Part 1

(i) Should IARC pursue the realization of a large multicentric clinical trial to investigate the potential impact of H. pylori eradication on stomach cancer incidence, including evaluation of:
   a) Reduction of stomach cancer or surrogates in different subgroups (age, sex, geographic location);
   b) Incidence of adverse events associated with treatment;
   c) Incidence of conditions potentially associated with eradication of H. Pylori (asthma, obesity, adenocarcinoma of the oesophagus);
   d) Cost effectiveness of the intervention.

(ii) What is the ideal design of the study?
   a) Cluster randomized trial with passive follow-up and stomach cancer as outcome;
   b) Individually randomized trial with detailed ascertainment of adverse events, close endoscopic follow-up and surrogate outcome.

(iii) What are the main ethical considerations to conduct such a trial?

Randomized controlled investigation of different surveillance strategies in colorectal cancer (CRC) screening

Currently, colorectal cancer (CRC) is the third most common cancer and the fourth most common cause of cancer deaths worldwide, with 1.2 million estimated cases and 609 000 estimated deaths in 2008. Based on demographic trends, the annual incidence is expected to increase by nearly 80% to 2.2 million cases over the next two decades and most of this increase will occur in the less developed regions of the world (62%). Current and previous trends in CRC incidence, based on data from cancer registries in selected countries suggest that the burden of disease in the currently less developed regions of the world may be even higher in 2030 if these countries continue their trends towards a more Western lifestyle with increased obesity, higher consumption of red meat, lower consumption of fruit and vegetables, and less physical activity.

In high-resource settings population-based screening is increasingly becoming a viable option for control of CRC. If diagnostic work-up indicates sufficient suspicion of CRC, colonoscopy (CS) is performed to clarify the need for treatment and to remove small lesions. Colonoscopic surveillance is a widely recommended practice for people identified by screening to have a sufficiently elevated risk of developing CRC to warrant a more intense protocol of prophylactic

examination than that offered by the screening programme. The underlying assumption is that the burden of CRC in this group of people can be more effectively and efficiently reduced by repeating colonoscopy over a lengthy period of time according to an agreed algorithm than by returning the respective people to the screening programme or to usual care.

The relative contribution of surveillance programmes to the overall impact of screening has not yet been determined in prospective studies in various screening settings. Furthermore, systematic implementation of CS surveillance has the potential to consume a significant volume of limited endoscopic resources which could otherwise be used for implementation and expansion of CRC screening programmes, or for improvement and capacity building of symptomatic care. Thus, surveillance on an inappropriate scale has the potential to prohibit implementation of nationwide CRC screening programmes due to unnecessary consumption of limited colonoscopic resources, particularly in medium-resource settings.

Less resource-intensive surveillance strategies have been recommended in the EU than in the USA. Clarification of the appropriate volume of surveillance in population-based colorectal cancer screening programmes would provide evidence crucial to the planning and effective implementation of CRC screening programmes, particularly in settings with limited resources. A randomized trial design in a large region served by a population-based screening programme and with different intervention arms corresponding, for example, to different CS surveillance intervals could be implemented in the framework of the programme as a randomized public health policy. This approach would lower the organizational costs of the study. Depending on local and national health policies, acceptable surveillance strategies should also be evaluated which deviate from widely recommended resource-intensive strategies.

Questions for the Scientific Council (EDP) – Part 2

We propose a multinational randomized controlled trial. Some of the arms of the study would involve a higher intensity of surveillance than that recommended in the EU quality assurance guidelines. However, some of the study arms would involve lower intensities of surveillance, particularly for people in whom screening results suggest low or moderate risk of future disease.

The rationale for this design is that the evidence base for surveillance in people of low or moderate risk is weak and the benefit is essentially limited to detection of cancer precursors, not early invasive cancer. Thus, even in a high resource setting it would be appropriate to provide only minimal surveillance.

(i) Do you agree that this rationale is sufficient to justify limited surveillance in some of the study arms?

(ii) If not, would it be appropriate to only conduct the study in low- or medium-resource countries with an appropriate burden of disease but only enough resources to implement a population-based screening programme with little or no surveillance?

(iii) Would the results of such a study be beneficial for your country?

Section of IARC Monographs (IMO) – Section Head, Dr Kurt Straif

Evolution, current path and future directions of the IARC Handbooks of Cancer Prevention

The mission of IARC is the global control of cancer, primarily through primary and secondary prevention, which is the most effective response to the rising burden of cancer, particularly in low- and middle-income countries (LMIC) where health services are least able to meet the impending challenge.

The first step in cancer prevention is to identify the causes of human cancer and what works in cancer prevention. The IARC Monographs are the point of reference for cancer causing agents. In 1995, the IARC Handbooks of Cancer Prevention were launched to complement the IARC Monographs' evaluations of carcinogenic hazards with evaluations of chemopreventive agents (NSAIDs, carotenoids, vitamin A, retinoids), preventive actions (use of sunscreens; weight control and physical activity; fruits and vegetables; cruciferous vegetables, isothiocyanates and indoles), effectiveness of screening (for cancers of the breast, and cervix) and on the effectiveness of tobacco control (reversal of risk after quitting smoking; smoke-free policies; tax and price policies). Since the inception of the series on average one volume per year has been developed.

Before becoming the first Head of the IARC Handbooks of Cancer Prevention, Dr Harri Vainio served as the Head of the Monographs for more than ten years and the working procedures and the evaluation scheme of the Handbooks closely mirror those of the Monographs. Still, the two programmes existed in parallel for the past 15 years.

There are also some asymmetries between the IARC Monographs and the Handbooks. While the Preamble to the Monographs states that "*Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.*", the Working Procedures for the Handbooks mention in "*Chapter 9. Recommendations: After its review of the data and its deliberations, the working group formulates recommendations, where applicable, for: further research and public health action.*"

More recently, the Handbooks have focused on tobacco control, and depended on ad hoc external funding. Today, the future of the Handbooks is open and it is now proposed to re-broaden the scope of the Handbooks into preventive agents and cancer screening and to place the responsibility for the future of the Handbooks into the section of the Monographs. The portfolio of expertise available in IMO, and procedures followed and tools used in developing IARC Monographs should benefit the development of new Handbooks.

Future topics of the Handbooks could include the evaluation of cancer screening, both first time (for cancers of the prostate, colorectum, or lung), as well as re-evaluations for cancers of the breast (where improvement of treatment outcomes for late stage breast cancer has led to questioning the effectiveness of screening), or cervix, (where new approaches in times of HPV vaccination have become available, including approaches – such as HPV testing – that might be particularly appropriate for LMIC). Similarly, an update of some of the Handbooks on preventive agents (e.g. aspirin, weight control and physical activity; fruits and vegetables) would be

warranted and new topics may soon be ready for first-time evaluations (e.g. Vitamin D, Vitamin B).

In the medium-term one might even consider merging of the IARC Monographs and the Handbooks: some of the established chemopreventive agents while reducing the risk of cancer in one site increase the risk of other cancers (e.g. tamoxifen and endometrial cancer), and some of the agents originally intended for chemoprevention turned out to increase the risk of cancer (e.g. combined oestrogen–progestogen menopausal therapy and breast cancer; vitamin E and prostate cancer). Conversely, some carcinogenic agents seem to reduce the risk of cancer in some sites (alcohol drinking and kidney cancer). This potential ambiguity extends to some of the priority agents for the Monographs programme and finally it is a question of perspective if a Working Group is tasked to evaluate the cancer preventive effect of weight control and physical activity or the carcinogenic effect of obesity and sedentary work.

Questions for the Scientific Council (IMO)

(i) Does the Scientific Council support the initiative to re-broaden the scope of the Handbooks into preventive agents and cancer screening and to place the responsibility for the future of the Handbooks into the section of the IARC Monographs?

(ii) At an IARC-internal discussion on the future of the Handbooks, the following topics have been considered as high priority:
   a) Effectiveness of screening for prostate cancer;
   b) Effectiveness of screening for colorectal cancer;
   c) Aspirin as a cancer-preventive agent.

(iii) Which agents would the SC consider of high priority for (re-)evaluation by the Handbooks?

(iv) Should future Handbooks continue to include recommendation for public health action?