International Agency for Research on Cancer

World Health Organization

Governing Council **GC/59/14**
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Auditorium

ACCEPTANCE OF GRANTS AND CONTRACTS

1. Post facto reporting

The Governing Council is invited to note the post facto reporting of grants and contracts accepted by the Director over €100 000 per annum, including sums passed to third parties, as detailed below.

Section of Cancer Surveillance (CSU)

1.1 Project title: **Making cancer data count: IARC strategies to support the development of population-based cancer registries in low- and medium-income countries for cancer control planning (GICR)**

Linking in with the global political agenda tackling noncommunicable diseases (NCDs), GICR is a multi-partner initiative coordinated by IARC providing measurable improvements in the coverage, quality and networking capacity of cancer registries in low- and middle-income countries (LMICs). Officially designated as IARC Regional Hubs for Cancer Registration, the centres aim to accelerate the availability and enhance the quality of data to inform national cancer control policies.

The project focuses on strategic development of the GICR and the Regional Hubs, the delivery of targeted training courses to develop local expertise, and the production of accompanying tools to enhance global statistics and assist with the planning and operations of cancer registry systems in LMICs defined in six Hub regions (1. Sub-Saharan Africa, 2. Northern Africa & Central and Western Asia, 3. Southern, Eastern and South-Eastern Asia, 4. Latin America, 5. The Caribbean and 6. The Pacific Islands).

In order to ensure coordination across the Regional Hubs, IARC coordinates a Hub Executive (HEX) whereby the principal investigators of the Hubs, IARC staff and other experts are able to exchange experiences to ensure best practice across the Hub network.

Donor:	German Federal Ministry for Health (BMG), Germany
Duration:	6 months
Funds for IARC:	€150 000 (US$ 168 161)
Funds for partners:	-
Total:	€150 000 (US$ 168 161)
Partners:	**n/a**

1.2 Project title: **International Cancer Benchmarking Partnership**

The overarching aim of the SurvMark-2 project is to understand the reasons for survival differences between countries in order to eliminate survival disparities in the near future. The approach is to develop a comprehensive and quality-assured set of country-specific indicators for benchmarking across countries. The comparative analyses undertaken will be the basis to identify factors that individually or collectively contribute to the observed survival differences for the seven cancers under study. The multi-disciplinary and team-based approach will require methodological, clinical and public health expertise from each of the participating countries. As the coordinating centre, IARC will harmonize the datasets to comply with international standards.

This project is expected to have impact on national cancer policies, to lead to recommendations that will enhance data quality and standardise data collection for international analyses, to pioneer novel methods on cancer outcomes to ensure more meaningful survival analyses and cross-country comparisons and to ensure better communication of prognosis to patients, clinicians and other stakeholders through the provision of a comprehensive of set of indicators, beyond traditional survival metrics.

Donor:	Cancer Research UK (CRUK), United Kingdom
Duration:	36 months
Funds for IARC:	€838 893 (US$ 890 545)
Funds for partners:	€443 407 (US$ 470 708)
Total:	€1 282 300 (US$ 1 361 253)
Partners:	Queen Mary University London (QMUL), United Kingdom, €184 824 (US$ 196 204)
	University of Leicester, United Kingdom, €258 583 (US$ 274 504)

Section of Environment and Radiation (ENV)

1.3 Project title: **Historical cohort study of cancer mortality among workers exposed to chrysotile asbestos in Asbest town, Sverdlovsk region, Russian Federation**

The main objective of the IARC-SRIOH (Scientific Research Institute of Occupational Health, Russian Federation) collaborative project initiated within the National Program for Elimination of Asbestos-Related Diseases is to more precisely characterize and quantify the exposure-response relationship for total and site-specific cancer risks associated with occupational exposure to chrysotile asbestos. In 2009, detailed requirements to conduct a large-scale historical cohort study on occupational exposure to chrysotile asbestos and cancer have been defined. The study is conducted at the JSC Uralasbest enterprise (Asbest town, Sverdlovsk region), at which a large number of workers with relatively long term exposure to chrysotile, and adequate number of years of follow-up with sufficient latency are available. During the period 2016-2017, the extraction of workers' information from company archives for the ascertainment of the cohort is completed as well as follow up utilizing the respective authorities' information on vital status and cause of death have started.

Donor:	Russian Ministry of Health (RMOH), Russian Federation
Duration:	12 months (further 24 months with additional budget are planned)
Funds for IARC:	€177 807 (US$ 198 224)
Funds for partners:	-
Total:	€177 807 (US$ 198 224)
Partners:	**n/a**

Section of Genetics (GEN)

1.4 Project title: **Molecular characterization of malignant pleural mesothelioma**

Malignant mesothelioma (MM) patients usually die within 2 years after diagnosis. MM is related to asbestos exposure, but a long latency exists between the exposure and the development of disease. As the peak of asbestos use is yet to exceed the latency window, MM incidence is expected to increase. The challenging diagnosis of MM and the frequent lack of suitable biopsies may leave doctors uncertain about the diagnosis. Well-differentiated papillary mesothelioma (WDPM), another tumour of mesothelial origin with a borderline malignancy, is often misdiagnosed as diffuse malignant mesothelioma. MM is treated with standard chemotherapy that does not significantly prolong survival in comparison to supportive care, probably because MM is usually not detected until symptoms arise, when surgery is no longer an option. The availability of a diagnostic marker for the early detection and more accurate diagnosis of the disease is an unmet need in the management of MM.

France has developed a strongly integrated network on MM. The MESOBANK currently contains biological specimens for more than 10,000 MM cases, with unique depth of etiological and clinical annotations. Taking advantage of this extraordinary collection, we propose to perform a comprehensive molecular characterization of MM by performing integrative analysis of genomic, transcriptomic, and epigenomic sequencing data, use the molecular-based classification for a more precise diagnosis of the disease, and a better characterization of the different histological types. We will also test the use of the identified somatic alterations for the early detection of this deadly disease that, if successful, will help identify candidate biomarkers for the early detection of MM.

Donor:	Institut National du Cancer (INCa), France
Duration:	36 months
Funds for IARC:	€536 185 (US$ 607 920)
Funds for partners:	€64 808 (US$ 73 478)
Total:	€600 993 (US$ 681 398)
Partners:	Centre Léon Bérard, France, €64 808 (US$ 73 478)

1.5 Project title: **Biomarkers of lung cancer risk**

Lung cancer is the cancer killing the highest number of people around the world. Because of the notable tobacco use, lung cancer is common in France, and with over 40,000 new cases occurring every year, France has the 7th highest lung cancer incidence rates worldwide. Whilst lung cancer survival rates are dismal overall, the prognosis for newly diagnosed cases is strongly influenced by disease stage. Increasing the proportion of cases with early stage disease at diagnosis could therefore have a major impact on the lung cancer mortality rates. Indeed, a large US lung cancer screening trial recently demonstrated that screening with low-dose computed tomography (CT) scans can reduce lung cancer mortality by 20%, albeit with important financial costs and high number of false positive screens. Subsequent studies have shown the importance of targeting those subjects with sufficiently high risk in order to increase the efficiency in CT screening. We hypothesize that it is possible to identify a limited panel of risk biomarkers and develop a lung cancer risk prediction model that substantially improves existing models in identifying those subjects that are most likely to benefit from screening. We will initially assay a wide range of promising circulating risk biomarkers, including markers such as immunobiomarkers, micro-RNAs (miRNAs), methylation markers and circulating tumour DNA, all of which have been implicated in lung cancer. All promising risk biomarkers will be measured on a common set of pre-diagnostic plasma or DNA samples from the European Prospective Investigation into Cancer and Nutrition (EPIC) study, including 396 lung cancer cases and smoking matched controls. Using the set of validated risk biomarkers, we will construct extensive risk prediction models and evaluate the extent to which they improve existing models. We believe that this project has unique translational opportunities to refine screening eligibility criteria and ultimately help to further reduce lung cancer mortality and improve screening efficiency.

Donor:	Institut National du Cancer (INCa), France, through Fondation ARC pour la Recherche sur le Cancer (ARC), France

Duration:	36 months
Funds for IARC:	€354 010 (US$ 375 807)
Funds for partners:	€155 792 (US$ 165 384)
Total:	€509 802 (US$ 541 191)
Partners:	Institut national de la santé et de la recherche médicale (INSERM), France, €155 792 (US$ 165 384)

1.6 Project title: **The role of germline and somatic DNA mutations in oral and oropharyngeal cancers**

Head and neck cancer is the world's sixth most common type of cancer. Most cancers of the head and neck are squamous cell carcinomas (HNSCC) and the majority affect the oral cavity or pharynx. Tobacco use and alcohol consumption are the major risk factors for HNSCC, and together account for about two thirds of the cases. Oral infection with human papillomavirus (HPV) is an important independent risk factor for primarily the development of oropharyngeal cancer (OPC), although only about 5% of other HNSCC sites appear to be associated with HPV. Candidate gene and genome-wide association (GWA) studies have identified multiple susceptibility loci for HNSCC but have generally been hampered by limited numbers of cases and controls and lack of information on HPV status. Similarly, although recently completed next-generation sequencing efforts have provided important information on the somatic alterations present in HNSCC and identified candidate therapeutic targets and driver mutations, only a limited number of HPV-positive tumours was included. Moreover, the genetic factors contributing to variation in disease outcome are not well characterized. The National Institute of Dental and Craniofacial Research (NIDCR) recently supported our proposal for a GWA study of OC and OPC consisting of over 6700 cases and comparable controls, genotyped by the Centre for Integrated Disease Research (CIDR) using the Illumina OncoArray. To maximize the potential of this initiative to improve understanding of the role of genetic factors in risk and prognosis of OC and OPC and aid development of effective screening, prevention, early detection and treatment strategies, our international research group will: evaluate the relationship between germline variants and both OC and OPC; evaluate the relationship between germline variants and risk of HPV-related OPC, assess associations between germline variants, environmental exposures, and the presence of driver somatic alterations in tumour DNA, and identify genetic prognostic markers for OC and OPC.

Donor:	National Institutes of Health/ National Institute of Dental and Craniofacial Research (NIH/NIDCR), USA
Duration:	60 months
Funds for IARC:	€546 552 (US$ 571 707)
Funds for partners:	€2 447 596 (US$ 2 560 247)
Total:	€2 994 148 (US$ 3 131 954)
Partners:	University of Pittsburgh, USA, €596 388 (US$ 623 837) University of North Carolina at Chapel Hill, USA, €1 395 785 (US$ 1 460 026) University of Toronto, Canada, €226 013 (US$ 236 415)

University of Bristol, United Kingdom, €118 847 (US$ 124 317)

German Cancer Research Center (DKFZ), Germany, €110 563 (US$ 115 652)

Section of Nutrition and Metabolism (NME)

1.7 Project title: **Biomarkers of dietary fatty acids, lipid metabolism and risk of ovarian cancer within the EPIC study**

Our main aim is to investigate the association between biomarkers of dietary exposure to fatty acids and endogenous metabolism and ovarian cancer (OC) risk in the EPIC cohort. In a second analysis, we will clarify whether the association between fatty acids and OC risk are mediated by inflammation pathways. The total EPIC cohort includes 519,978 participants from 23 centres in 10 European countries. For this project, we will design a case-control study nested within the EPIC cohort among women who completed dietary questionnaires and provided blood samples. During the follow-up, 1,075 women with incident invasive epithelial OC were identified. For each case subject, two matched controls will be chosen randomly among cohort subjects without cancer. Plasma phospholipid fatty acid levels will be determined through gas chromatography methodology at IARC. The proposed study should improve our understanding of OC aetiology, for which there is no effective early detection. This knowledge will allow developing more effective public health policies for OC prevention targeted on dietary fatty acids.

Donor:	Institut National du Cancer (INCa), France
Duration:	36 months
Funds for IARC:	€341 262 (US$ 362 274)
Funds for partners:	-
Total:	€341 262 (US$ 362 274)
Partners:	**n/a**

1.8 Project title: **Immunity, inflammation and breast cancer risk in the EPIC cohort**

The role of the immune system in the promotion of tumour growth is now well recognized and inflammation has been defined as a hallmark of cancer. Chronic inflammation contributes to both the initiation and promotion of cancer as inflammatory mediators can cause genomic instability by increasing the production of free radicals which can, in turn, lead to DNA damage. Although the role of the immune system in tumour promotion was first demonstrated for cancers such as lymphomas, melanomas or lung cancers, experimental data now suggest that the infiltration of leukocytes can promote the development of breast cancers. Chronic inflammation is also a well-established characteristic of obesity, a known risk factor for postmenopausal breast cancer. In the last decades, evidence from epidemiological studies has accumulated that chronic inflammation could favour cancer development and prospective studies have shown that not only localized, organ-specific inflammation, but also systemic inflammation could be associated with carcinogenesis. We propose to address the hypothesis that factors involved with immune function

and low-grade inflammatory states are related to breast cancer risk. The objective of the project will be to examine if elevated blood concentrations of Th1 and Th2 cytokines as well as adipokines are associated with increased breast cancer risk, overall and by breast cancer subtypes. In addition, we will examine and quantify the relationships of these biomarkers with variable degrees of adiposity and physical activity, and with serum levels of other metabolic markers. The findings from this research project will contribute to the available knowledge of the association between excess weight and obesity and breast cancer risk, and should help clarify the mechanisms underlying this relationship. In terms of prevention, our results should give support to the reduction of chronic inflammation caused by obesity.

Donor:	Institut National du Cancer (INCa), France
Duration:	24 months
Funds for IARC:	€352 803 (US$ 374 525)
Funds for partners:	-
Total:	€352 803 (US$ 374 525)
Partners:	**n/a**

1.9 Project title: **Impact of chronic multi-mycotoxin exposure in Europe on cancer incidence: a basis to develop future public health strategies**

Mycotoxins are fungal toxins, estimated by the Food and Agricultural Organization (FAO) to contaminate 25% of the world's most frequently consumed foods and feeds. Several fungi may co-occur on crops, resulting in co-occurrence of multiple mycotoxins. Given the ubiquity of many fungi worldwide, an urgent need exists for a coordinated international response to the problem of dietary mycotoxins. In terms of chronic toxicity, mycotoxins are estimated to be the most hazardous food contaminants. IARC identifies aflatoxins B1, G1, and M1 as human carcinogens, while other mycotoxins are possibly or probably carcinogenic (e.g. ochratoxin A and fumonisins). The recognition of multiple mycotoxins having a potentially increased carcinogenic effect, over singularly present mycotoxins, is also echoed in more recent research and review papers. Consumed with food, mycotoxins most commonly affect the liver, where they are metabolized, though not always inactivated. Further down the gastro-intestinal tract, mycotoxins and their active metabolites may interact with colon cancer cells. It is imperative to comprehensively investigate the adverse health effects of mycotoxin exposure in Europe, more specifically, its carcinogenic potency, by means of cohort data. Although some studies reported country-specific intakes of mycotoxins, comparable information on dietary mycotoxin intakes across European countries has never been reported, and mycotoxins have never been linked to European cohort dietary data. The hypothesis is that high intakes of multiple mycotoxins could be associated with

an increased risk of developing hepatocellular (HCC) and colorectal carcinomas. The aim is to assess associations between single and multiple mycotoxin intakes in the full EPIC cohort, and HCC and colorectal cancer risks. A secondary aim is to elucidate the possible pathways and routes of external dietary and internal metabolized mycotoxin exposures, and their possible effect on HCC and colorectal cancer risks using nested case-control studies in EPIC.

Donor:	Fondation de France (Fdf), France
Duration:	24 months
Funds for IARC:	€204 000 (US$ 222 951)
Funds for partners:	-
Total:	€204 000 (US$ 222 951)
Partners:	**n/a**

1.10 Project title: **A pooling project on alcohol use and risk of cancers with inconsistent prior evidence, with an emphasis in non-smokers**

The consumption of alcohol has been identified as one of the top-10 risks contributing to the worldwide burden of disease. Alcohol consumption is responsible for about 2.7 million annual deaths and 3.9% of the global burden of disease. In 2012, the IARC Monograph program reviewed the epidemiological evidence on the possible association between alcoholic beverage consumption and cancer at 27 anatomical sites, and reported that cancers of the upper digestive tract (oral cavity, pharynx, larynx, oesophagus), liver, colorectum and female breast are causally related to the consumption of alcoholic beverages. Whereas the association of these specific cancer sites with alcohol use has been repeatedly observed, the evidence of the link with other sites, primarily prostate and pancreas, but also kidney, melanoma, thyroid, and Hodgkin's (HL) and non-Hodgkin's (NHL) lymphomas is either inconsistent or sparse. Despite the importance in human carcinogenesis, research on alcohol and cancer remains limited in terms of epidemiological and experimental settings. In collaboration with 36 cohort studies including about 2.8 million women and men, we propose an exhaustive investigation on alcohol use and cancers of the prostate, pancreas, kidney, and thyroid, melanoma, HL and NHL in non-smokers to evaluate the associations between lifetime alcohol use and age at drinking initiation and to evaluate specific patterns of alcohol intake, including binge drinking. Our research on the role of alcohol at low doses will have an important public health impact.

Donor:	National Institutes of Health/ National Institute on Alcohol Abuse and Alcoholism (NIH/NIAAA), USA
Duration:	48 months
Funds for IARC:	€586 990 (US$ 651 487)
Funds for partners:	€1 073 694 (US$ 1 191 669)
Total:	€1 660 684 (US$ 1 843 156)
Partners:	Harvard T.H. Chan School of Public Health, USA, €1 005 425 (US$ 1 115 899)
	Brigham and Women’s Hospital, Harvard Medical School, USA, €68 269 (US$ 75 770)

2. Prior approval for projects over €500 000 per annum

The Governing Council is invited to consider, for approval, projects submitted over €500 000 per annum, excluding sums passed on to collaborating institutions, and projects that require more than €100 000 per annum, excluding the principal investigator's staff costs, from the IARC regular budget, as detailed below.

Please note that the following project has been provisionally approved by the Chairperson of the Governing Council.

Section of Genetics (GEN)

2.1 Project title: **Mutographs of cancer: discovering the causes of cancer through mutational signatures**

Many common cancers exhibit major differences in incidence between different geographical areas and trends over time. Therefore, important causes of cancer and opportunities for prevention remain to be identified. Molecularly, changes in the DNA within cells called somatic mutations drive cancer development. Different patterns of somatic mutation, known as "mutational signatures", are generated by the different environmental, lifestyle and genetic factors. For example, tobacco smoke and ultraviolet radiation in sunlight both cause cancer by producing somatic mutations; however, the particular mutational signature caused by tobacco smoke chemicals is found in lung cancers and the distinct mutational signature of ultraviolet light is found in skin cancers. Recently, through analysis of the DNA sequences of many thousands of cancers of diverse types from across the world, approximately 40 different mutational signatures have been reported. However, the environmental, lifestyle, genetic or other potential causes of many of these mutational signatures are unknown. The overall goal of our work is to advance understanding of the causes of cancer through studies of mutational signatures. We will investigate whether different mutational signatures in the DNA of cancers explain geographic differences in cancer incidence. We will identify specific causes of mutational signatures by sequencing the DNA of rodent cancers and cultured human cells experimentally exposed to 150 cancer-causing agents, thus assembling a compendium of mutational signatures associated with known causes of cancer. We will investigate whether mutational signatures in the DNA of normal cells can be used to understand and monitor cancer-causing exposures in healthy people by sequencing the DNA of normal lung, kidney, liver and blood from people who have been exposed to cancer-causing agents. This work may lead to new approaches to prevent it and provide opportunities for more effective application of therapies.

Donor:	Cancer Research UK (CRUK), United Kingdom through Wellcome Trust Sanger Institute, United Kingdom
Duration:	60 months
Funds for IARC:	€5 297 206 (US$ 5 623 361)
Funds for partners:	€19 121 890 (US$ 20 299 247)
Total:	€24 419 096 (US$ 25 922 608)
Partners:	Wellcome Trust Sanger Institute, UK, €16 605 633 (US$ 17 628 060)
	University of California San Francisco, USA, €1 568 729 (US$ 1 665 318)
	King's College London, UK, €947 528 (US$ 1 005 869)

3. Interest income from grants

In accordance with the standing authorization provided to the Director under resolution GC/55/R23 and the conditions set forth in the signed agreements, interest income totalling €5716 was apportioned to three grants in 2016. Details are provided in the table below.

Grant No.	Project	Donor	Interest (in euros)
100401	Monitoring HPV vaccination and HPV screening programs to promote sustained implementation in low and middle income countries	Bill and Melinda Gates Foundation	1 392
100639	Extended Follow-up of the Participants of IARC-INDIA HPV Vaccination Study to Evaluate the Effectiveness of one, two and three Doses of Quadrivalent HPV Vaccine in Preventing Cervical Neoplasia	Bill and Melinda Gates Foundation	4 320
100705	ABC-PC: African Breast Cancer – Pathology Course	Susan G. Komen Breast Cancer Foundation	4
Total interest income apportioned to grants			**5 716**