International Agency for Research on Cancer

World Health Organization

Governing Council **GC/64/10**
Sixty-fourth Session 29 March 2022

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By Web conference

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, for the period 16 March 2021 to 15 March 2022, as detailed below.

Cancer Surveillance Branch (CSU)

1.1 Project title: **Targeting Childhood Cancer through the Global Initiative for Cancer Registry development (Year 2)**

In recognition of the shared mission to improve the outcomes of childhood cancer, St. Jude Children's Research Hospital (SJCRH) and the International Agency for Research on Cancer (IARC) recognize a common goal to implement a bilateral childhood cancer collaborative initiative through the GICR. The aims of this effort include (1) Expanding and improving cancer control data; (2) Developing educational strategies to strengthen the cancer registry workforce globally at scale; (3) Conducting relevant epidemiologic and health economics research.

The three workstreams are developed in working group. The objective of the Implementation Working Group is to further engage with four target countries (Georgia, Mexico, South Africa and Vietnam) to strengthen population-based childhood cancer surveillance.

The Education Working Group develops and standardized GICRNet teaching material, organises two regional courses, translates the teaching material to Spanish and French and disseminates education material and awareness to low- and middle-income countries. E-learning module is being planned. Several objectives are pursued in the Research Working Group. Registration standards and classification of CNS tumours is developed to improve global comparability of data. A review of the barriers and solution for international data sharing is elaborated and followed by a proposal for an easier access to childhood cancer data. Economic aspects of childhood cancer are being assessed through a systematic review of publications on financial hardship and a development of a tool to estimate costs of childhood cancer registration. This multiannual initiative is be renewed annually.

Donor:	St Jude Children's Research Hospital (US)
Duration:	12 months
Funds for IARC:	€236 135.14 (US$ 280 779.00)
Funds for partners:	n/a
Total:	€236 135.14 (US$ 280 779.00)
Partner:	n/a

Epigenomics and Mechanisms Branch (EGM) and Environment and Lifestyle Epidemiology Branch (ENV)

1.2 Project title: **Origins and causes of childhood cancer**

The PEDIAC project brings together eleven teams of basic research scientists from distinct major national cancer centres with expertise spanning a wide research area, including epidemiology, immunology, physiological modeling, genetic analyses and molecular biology of pediatric tumour cells. This consortium stems from a scientific program outside the usual French funding calls and will develop a 4-year pluri-disciplinary research program taking into consideration pediatric cancer causes from the macroscopic environmental level all the way to the molecular level driving tumour cell abnormal properties on different pediatric cancer entities.

PEDIAC's main research objective is to understand the causes and origins of different cancer subtypes at specific ages during childhood. Epidemiological and genetic studies already indicate that these specificities may result from environmental exposure to risk factors or from genetic predisposition. Also, recent experimental evidence indicate that specific pre or post-natal periods, as well as certain type of cells, are particularly sensitive to the oncogenic properties of the genetic alterations found in pediatric cancer. However, the precise knowledge of molecular bases underlying this peculiar sensitivity is generally lacking and need to be established in appropriate models accounting for the importance of the communication between abnormal cells and the surrounding cells.

The PEDIAC project is divided into three main aims: 1-Identify additional risk factors through in-depth analysis of epidemiological data and genetic analyses of immune regulatory processes, 2-Understand how the changes in the properties of cells during pre and post-natal period impact their sensitivity to genetic alteration frequently found in pediatric cancers, and 3-Develop novel and better models to study how pediatric cancer cells interact within their local cellular environment.

Through these studies, we aim at identifying potentially preventable risk factors and novel markers of genetic predisposition to cancer. The comparison of tumours from patients with models reproducing more closely the situation found in patients will allow the identification of active molecular mechanisms specific to pediatric tumour cells. Together, an improved knowledge of these factors will provide tools to better prevent cancer development or help diagnosis and develop future more efficient and less toxic therapeutic opportunities.

Donor:	Institut National du Cancer (FR)
Duration:	48 months
Funds for IARC:	€ 613 376.00 [€343 396.00 for EGM; €269 980.00 for ENV]
Funds for partners:	€3 086 624.00
Total:	€3 700 000.00
Partners:	Institut National de la Santé et de la Recherche Médicale (FR), Hôpital Universitaire Necker-Enfants malades (FR), Centre Léon Bérard (FR), Institut Imagine (FR), Institut Curie (FR), Institut Gustave Roussy (FR)

Environment and Lifestyle Epidemiology Branch (ENV)

1.3 Project title: **ABC-DO-Plus Maternal orphans and triple negative genomics / ABC-DO-Plus: Intergenerational mortality impacts and mutation spectrum of breast cancer**

The ABC-DO findings on survival have documented extremely low three-year breast cancer survival, at 50% across the entire cohort. The 800 deaths in this three-year survival analysis were associated with two features which form the focus of this supplement.

First, cancer deaths led to immense intergenerational effects of cancer in terms of the number of children who become maternal orphans. The loss of a parent can have long-term impacts on a child's life, with regard to his mental and physical health, education level and socioeconomic status. However, this intergenerational effect is rarely given attention, and has never been quantified globally, in part because most cancer deaths in high-income countries (HIC) occur in older persons when their children are already adults. In Low-to-Middle-Income Country (LMICs), the young population demographic and low survival imply that, when middle-aged women die of cancer, they often leave behind maternal orphans, i.e. children (<18 years) who have lost their mother. This study aims at estimating the global number of orphans due to maternal deaths from cancer in 2020. We will explore the number of orphans by country and cancer type to determine the main cancers contributing to these numbers and the regional disparities.

Second, deaths disproportionately affect women with triple negative breast cancer (TNBC) which were present in one in four women in Southern Africa. Breast cancers present with different mutation profiles called mutational signatures that have been identified in many tumour types, some of which have been linked to specific exposures or mechanisms. However, for the majority, we have no clear understanding. Studies of the mutational signatures and pathways in TNBC of African breast cancer patients, and comparison to the identified signatures in European women, may reveal reasons for the particularly low survival. In this supplement we propose to examine the exome of 25 ABC-DO TNBCs from Nigeria. Nigerian tumours have been selected because the excess of TNBC may be most pronounced in this region of Africa. Further, in the ABC-DO survival estimates, Nigeria had the lowest survival which may be driven by distinct tumour sub-types. We will examine the potential link between specific mutational signatures and breast cancer risk factors already collected through questionnaires which may in turn reveal mechanisms of action/origin of the mutation profiles.

Donor:	National Institutes of Health - National Cancer Institute (US)
Duration:	12 months
Funds for IARC:	€269 733.26 (US$ 328 943.00)
Funds for partner:	n/a
Total:	€269 733.26 (US$ 328 943.00)
Partner:	n/a

1.4 Project title: **Cancer Risk Attributable to the Body Art of Tattooing**

Despite the high population prevalence of tattoos (14% in France, upward trend), knowledge on health consequences of tattoos is scarce and tattoos are generally regarded as harmless to health. Previous research showed that tattoo pigments contain carcinogenic substances (PAHs, PAAs, metals) and migrate from the skin into the body, first the lymph nodes and from thereon presumably to other organs. While carcinogenicity after oral and respiratory uptake of the abovementioned substances has well been studied, their subcutaneous exposure, as in the case of tattoos, remains largely unexplored and epidemiological

studies are largely missing. Tattoo-related problems have also been highlighted in case reports of dermatologists. The present project aims to investigate a potential tattoo-induced cancer risk, in particular skin and lymph node cancer, as well as tattoo-related dermatological and immunological consequences, by a longitudinal epidemiological study within in the French national cohort Constances (population size: 220 000). An additional tattoo exposure questionnaire is sent to all Constances participants who reported being tattooed in the 2020 Constances repeat questionnaire.

Donor:	Institut National du Cancer (FR)
Duration:	48 months
Funds for IARC:	€448 741.00
Funds for partner:	€ 39 312.00
Total:	€488 053.00
Partner:	Université Paris Est Créteil Val de Marne (FR)

Early Detection, Prevention, and Infections Branch (EPR)

1.5 Project title: **E6/E7 oncoproteins for risk stratification of women living with and without HIV attending HPV-based cervical screening**

Cervical cancer is the 4th most common cancer in women globally, and the leading cause of cancer-related deaths in women in most African countries, mainly in sub-Saharan populations severely affected by the human immunodeficiency virus (HIV) epidemic. Scale-up of HPV-based cervical screening is needed to achieve global WHO 2030 cervical cancer elimination goals, and feasible screening approaches suitable for neglected high-risk populations should be proposed. This is an Administrative Supplement for grant 5UH3CA202730-04, "Development and validation of a multi-type HPV E6/E7 oncoprotein test for cervical cancer screening and triage in low- and middle-income countries". The scope of the parent grant is to evaluate the 8-HPV type E6/E7 Cervical Test as triage of HPV positives for cervical intraepithelial neoplasia grade 2 or worse (CIN2+) detection in LMIC, and this supplement will permit additional validation of the 8-HPV type E6/E7 Cervical Test in high-risk populations, notably in women living with HIV (WLHIV) and in HIV negative women with very limited access to health care. The proposed project will analyze biological samples, epidemiological and clinical data from women participating in the CESTA ("Cervical Cancer Screening and Treatment Algorithms using Human Papillomavirus Testing") studies targeting mainly WLHIV in South Africa and HIV negative women in Senegal. CESTA studies aim at evaluating the efficacy of HPV testing followed by treatment of HPV positives with or without triage with visual inspection of the cervix with acetic acid (VIA) and treatment of VIA positives. The primary aims of this supplement are to: 1) to investigate the role of the 8-HPV type E6/E7 Cervical Test within HPV-screen-and-treat strategies, and, 2) to estimate the sensitivity and specificity of the 8-HPV Type OncoE6/E7 Cervical Test as triage for HPV positives to detect CIN2+ among women living with HIV (WLHIV). We hypothesize *i)* that the balance between overall sensitivity and specificity of combining a high sensitive HPV test with the 8-HPV type E6/E7 Cervical Test as triage of HPV positives will lead to identifying and treating most CIN2+ lesions present on screening, while avoiding substantial overtreatment particularly in WLHIV in whom HPV infection is extremely common, and, *ii)* that the 8-HPV type E6/E7 Cervical Test characteristics will allow its rapid incorporation in laboratories serving high-risk populations, increasing the feasibility of scaling-up HPV-based cervical screening in less-resourced settings.

Donor:	National Institutes of Health - National Cancer Institute (US)
Duration:	12 months
Funds for IARC:	€246 000.00 (US$ 300 000.00)
Funds for partners:	€ 41 000.00 (US$ 50 000.00)
Total:	€287 000.00 (US$ 350 000.00)
Partners:	Instituto Nacional de Cancerología Bogotá (CO), Universidad de Antioquia Medellin (CO), Instituto de Investigaciones en Ciencias de la Salud – Universidad Nacional de Asunción (PY), Universidad Nacional Autónoma de Honduras Tegucigalpa (HN), Epidemiólogico Guanacaste Puntaneras (CR), Juan Mural Instituto Nacional de Enfermedades Infecciosas-ANALIS Dr. Malbrán Hospital Posadas Buenos Aires (AR), Universidad San Francisco Xavier de Chuquisaca Sucre (BO), Centre Hospitalier Aristide le Dantec (SN), University of Kwazulu Natal (ZA)

1.6 Project title: **Economic evaluation of treatment of cervical precancers in screen and treat setting**

Screen-and-treat approaches to cervical cancer prevention have become standard practice in many low- and middle-income countries (LMICs), where they have been shown to reduce loss-to-follow-up and improve clinical outcomes. In most sub-Saharan African countries, screening is conducted by visual inspection with acetic acid (VIA), with screen-positive women receiving cryotherapy for treatment. Thermal ablation (TA) has recently been endorsed by the World Health Organization as an alternative treatment strategy for LMICs, with similarly high efficacy to cryotherapy.

We completed a pilot UH2 phase randomized controlled trial (RCT) to evaluate the effectiveness of TA compared to the current standard treatment (cryotherapy) and to LLETZ when used as part of a VIA-based screen-and-treat programme in Zambia. A total of 750 VIA-positive women eligible for ablative treatment were randomly allocated to receive treatment by one of the above techniques (TA, cryotherapy, or LLETZ) in a 1:1:1 ratio. Every participant was tested for Human Papillomavirus (HPV) at baseline and, if the baseline HPV test was positive, at the 12-month follow up visit. Results from the pilot phase indicate lower pain and cramping with TA (5.2%) than cryotherapy (13.7%) or LLETZ (6.6%). Treatment success rates at 6 months were similar across the three arms (using a combined endpoint of HPV negativity and VIA negativity): 64.1% in the TA arm, 60.0% in the cryotherapy arm, and 63.8% in the LLETZ arm (p=0.31). Nearly 50% of the recruited women were living with HIV. In January 2019, we transitioned to a UH3 phase RCT to recruit an additional 1000 women in each arm. [Grant Number: 1UH2CA202721-01]

To inform policy decision-making on cervical cancer treatment, there is a need for economic research comparing TA to cryotherapy or LLETZ in treatment of cervical neoplasia. For settings with high HIV prevalence, understanding of how clinical and economic outcomes may differ by HIV status is also greatly needed. While some prior studies have assessed costs and cost-effectiveness of LEETZ and cryotherapy in HIV-positive women, or screen-and-treat programmes using cryotherapy in all women, and HIV-infected women, none have compared these standard treatments to TA or directly compared outcomes in HIV-positive and HIV-negative women. Our ongoing RCT provides a unique opportunity to address this gap. We propose to conduct a cost-effectiveness and budget impact evaluation within our RCT to compare the three treatment arms. As the screening paradigms in LMICs will also gradually shift towards HPV detection - based screening, we will also collect HPV test related data to evaluate alternative screen-and-treat paradigms with HPV-based screening. The WHO Cervical Cancer Prevention and Control Costing Tool (C4P) aimed to aid

decision making in cervical cancer control strategies (https://www.who.int/immunization/diseases/hpv/cervical_cancer_costing_tool/en/) will be used to facilitate analysis and synthesis of cost data utilizing the data collected from the RCT and routine health services.

Donor:	National Institutes of Health - National Cancer Institute (US)
Duration:	12 months
Funds for IARC:	€287 000.00 (US$ 350 000.00)
Funds for partners:	n/a
Total:	€287 000.00 (US$ 350 000.00)
Partner:	n/a

1.7 Project title: **Artificial intelligence-assisted decision-making to improve women's participation to cervical cancer screening in Occitanie Region-France**

The French organized population-based cervical cancer screening programme shifted from cytology-based to HPV-based screening strategy, every five years, starting at 30 years of age, in August 2020. In the new programme, invitations are sent to women to have HPV testing done, by a gynaecologist, a general practitioner, or a midwife, in private clinic or health centre, family planning centre or hospital. HPV self-sampling was also made available as an additional approach. However, less than 20% of French women performed vaginal self-sampling when a kit was sent to their home. Women with lower income and educational levels participate less to cervical screening. A variety of personal, practitioner, test-related and logistical barriers negatively impact the screening participation of French women. Key barriers to participation could be addressed by overcoming disparities in HPV-related knowledge and perceptions about cervical cancer screening.

The project aims to improve HPV self-sampling "return" rate as well as the proportion of invited women "well managed". We plan to conduct a two-arm cluster randomized-controlled trial nested within the French organized cervical screening programme among non-responders living in deprived areas in Occitanie Region-France. A cluster is defined by aggregated units for statistical information (*IRIS*) and which refers to the target size of 2000 inhabitants per basic unit. Only IRIS classified 4 and 5 according to the French version of the European Deprivation Index will be included. The intervention consists in providing, through multiple mobile channels, a multilingual decision aid designed for low-educated women, as well as a home-delivered HPV self-testing kit. The decision aid tool will be incorporated into an artificial intelligence-based ChatBot. Our approach aims at enhancing the efficiency of the existing organized programme without substantial modification of its structure. The overall goal is to increase women's adherence to cervical cancer screening and reduce inequalities, which means decreasing their risk of cervical cancer or late diagnosis, thereby reducing the social and economic consequences of cervical cancer and improving quality of life indices with immediate economic benefits to society.

Donor:	Institut National du Cancer (FR)
Duration:	48 months
Funds for IARC:	€453 902.00
Funds for partners:	€ 29 224.00
Total:	€483 126.00
Partners:	Centre Régional de Coordination des Dépistages des Cancers – Occitanie (FR), University of Brest (FR)

1.8 Project title: **Proposal for a collaborative initiative between IARC and Department of Health of Ireland to support Ireland in delivering an exemplar Cervical Cancer Screening Programme for their population**

The collaborative initiative between IARC and Department of Health of Ireland will prepare a strategic guidance for the proposal for the cervical cancer screening programme to strengthen the in-built system of quality improvement and regain public trust in the programme.

The strategic guidance to be prepared in collaboration with all relevant stakeholders and experts will include consideration of the following tracks:

- Track 1: Strategies for embedding continuous quality improvement and transparency within the cervical cancer and pre-cancer screening services
- Track 2: Appropriate communications strategies with the public and screening participants related to benefits, inadequacies and harms of cervical cancer and pre-cancer screening
- Track 3: Improving capacity of staff and managers associated with screening programme in open and effective communication related to benefits, inadequacies and harms of screening
- Track 4: Legal implications & ethics of cervical cancer screening.

Donor:	Healthy Ireland - Department of Health (IE)
Duration:	9 months
Funds for IARC:	€200 000.00
Funds for partners:	n/a
Total:	€200 000.00
Partner:	n/a

1.9 Project title: **Improving cancer care coordination and screening in Latvia and Slovakia**

Latvia and Slovakia are lagging behind among the EU Member States regarding their performance indicators related to the cancer care continuum and particularly their cancer screening programmes. In Latvia, cancer registries are outdated and have not produced reliable statistics in the last two years (only EU country in this situation). Data registration platforms are incapable of assuring data capture and exchange corresponding to the current requirements. Most importantly, there is a lack of clearly defined responsibilities that have frequently been migrating between public institutions; several ministries contribute to cancer policies, but the coordination level is not always satisfactory. Moreover, in Latvia, there is no accredited centre for cancer care in charge of strategic planning. On the other hand, in Slovakia, the Ministry of Health intends to prepare a new National cancer action plan for 2021-2025, in line with the "Europe's Beating Cancer Plan". The plan aims to reduce the number of new cancer cases and death; and at improving the quality of life of cancer patients through the systematic and equitable implementation of evidence-based strategies for prevention, early diagnosis, diagnosis, treatment, rehabilitation, supportive and terminal care, and research into finding innovative solutions and evaluating results. The overarching goal of this proposal is to propose a strategic plan and a roadmap that would contribute to the improvement of early detection of cancer and reduction of cancer mortality in both countries, specifically by improving the cancer registry, cancer screening programmes and aiming for comprehensive cancer care and research infrastructure/network accreditation in Latvia; and by improving coverage and quality of breast, cervical and colorectal cancer screening programmes and better awareness of stakeholders in Slovakia.

Donor:	European Commission - Structural Reform Support (BE)
Duration:	24 months
Funds for IARC:	€830 000.00
Funds for partner:	n/a
Total:	€830 000.00
Partner:	n/a

Genomic Epidemiology Branch (GEM)

1.10 Project title: **InterLymph Consortium: interrogating pleiotropy and gene by environment interactions among hematopoietic malignancies**

Most lymphomas and multiple myeloma (MM) are malignancies resulting from the unrestrained clonal proliferation of B-cells at different stages of maturation. For nearly two decades, the International Lymphoma Epidemiology (InterLymph) Consortium has systematically uncovered genetic and non-genetic lymphoma and MM risk factors. We aim to build upon nearly 20 years of successful collaboration within the InterLymph Consortium to undertake the largest genome-wide association study (GWAS) of lymphomas and MM to date, to assess the performance of polygenic risk scores for lymphomas, and to identify gene-environment interactions associated with disease susceptibility. This will address key questions: specifically, can we fully elucidate the genetic variants involved in susceptibility MM, HL, and NHL subtypes? How do the genetic profiles overlap? How do these profiles interact with the environmental risk factors? With further precision, can factors be combined to assist in risk prediction? In Aim 1, we will undertake the largest genome wide association study (GWAS) to date of ~60,000 lymphoma cases, including HL (N=~6,700), NHL (N=~36,000) and MM (N=~16,000) and over 197,000 controls. In Aim 2, we will develop polygenic risk scores (PRS), including conducting a validation of the PRS in an independent series of 13,700 lymphoma patients. In Aim 3, we will evaluate GWAS and subtype-specific PRS in the context of select environmental exposure data to gain novel insight into exposure-disease relationships and potentially uncover novel susceptibility loci which act only in the presence of specific environmental triggers. Finally, in Aim 4, we will create a platform hub for the InterLymph Consortium. This platform, called the Data Coordinating Center (DCC), will ensure that the field's most pertinent, cutting-edge hypothesis driven research questions can be applied within the resources of the InterLymph Consortium. Through this project, we aim to activate the collective intelligence and resources of the InterLymph researchers in order to expand our understanding of how genetic variants and the environment influence risk of lymphomas and explore how this may assist clinical practice. Public health relevance: Successful completion of these aims will result in user-friendly, accessible, centralized platform of genetic and environmental data across the international scientific community that would promote collaboration and new scientific discoveries. These data will be critical for generating important insights regarding the fundamental biology of lymphomag.

Donor:	National Institutes of Health - National Cancer Institute (US)
Duration:	60 months
Funds for IARC:	€ 460 284.22 (US$ 542 788.00)
Funds for partners:	€1 857 767.88 (US$ 2 190 764.00)
Total:	€2 318 052.10 (US$ 2 733 552.00)
Partners:	University of South Carolina (US), Memorial Sloan Kettering Cancer Center (US), Beckman Research Institute of the City of Hope (US), Danish Cancer Society Research Center (DK)

1.11 Project title: **Blood-based high-risk HPV DNA detection for prognostication and post-treatment monitoring of oropharyngeal squamous cell carcinoma patients**

Infection with human papillomavirus (HPV) has been identified as an important and independent risk factor for the development of oropharyngeal cancer (OPC). Despite the improved clinical outcome of HPV-positive OPC, up to 25% of cases will develop recurrent or distant metastatic disease. The monitoring of tumour progression and treatment response by physical and imaging examinations are insufficient to detect asymptomatic lesions, delaying salvage treatment interventions and dramatically reducing chances of cure. Therefore, there is an urgent need for tools that can guide precision therapy and improve outcome by predicting patients with unfavourable prognosis and improving monitoring of treatment response and detection of minimal residual disease (MRD). This study will explore the clinical utility of the detection of HPV circulating DNA in blood samples from HPV-positive OPC patients collected prior to treatment and during follow-up visits. We expect to provide resources to improve survival rates and reduce treatment related morbidity by validating methods to better stratify patients according to outcome and improve patient management through a more efficient monitoring of MRD during patient surveillance.

Donor:	Institut National du Cancer (FR)
Duration:	36 months
Funds for IARC:	€291 686.90
Funds for partner:	€159 710.10
Total:	€451 397.00
Partner:	Institut National de la Santé et de la Recherche Médicale (FR)

Nutrition and Metabolism Branch (NME)

1.12 Project title: **Examining the role of the immune system in colorectal cancer development**

Specific immune responses, such as chronic inflammation and immune activation from allergies, may play a role in colorectal cancer (CRC) development. Experimental studies implicate chemokines and cytokines as mediators of the inflammation and CRC association; however, human data linking pre-diagnostic circulating levels of these proteins with CRC are limited. For the potential allergies and CRC relation, previous studies were limited by the narrow information on allergies collected, with allergy diagnoses over time, age of diagnosis, and allergy medication use unmeasured.

The first objective of this project is to examine the relationships between circulating levels of inflammation markers and CRC development. Therefore, we investigate the relationships between pre-diagnostic circulating levels of 92 inflammatory-related proteins (including chemokines and cytokines) and CRC risk in 1000 cases and 1000 controls from the EPIC Study. In addition, the potential causality of the association

between circulating inflammatory biomarker levels and CRC risk needs to be explored. Using genetic consortium data, we will conduct Mendelian randomization (MR) analyses examining the associations between genetically-predicted circulating levels of chemokines/cytokines and CRC.

The second objective is to examine the role of allergies in CRC development. To achieve this, we need to investigate the relationships between CRC risk and diagnoses of asthma, hay fever, and eczema in a pooled analysis of >600 000 participants from the E3N and UK Biobank studies. We also need to conduct MR analyses examining the associations between allergies and CRC, using genetic consortium data.

This project offers powerful and novel insights into how immune system perturbations may influence CRC risk.

Donor:	Institut National du Cancer (FR)
Duration:	48 months
Funds for IARC:	€346 326.00
Funds for partner:	€ 98 423.00
Total:	€444 749.00
Partner:	Institut Gustave Roussy (FR)

1.13 Project title: **Obesity and endometrial cancer: integrative molecular tools to identify the underlying causal pathways**

Obesity has been shown to be a major risk factor for endometrial cancer, causing up to 60% of the cases, the first gynaecological cancer in terms of incidence in developed countries. As a consequence of the obesity epidemic, the incidence of endometrial cancer has been growing in the past decades in both high- and low-income countries. The mechanisms linking obesity to endometrial cancer are ill understood and the impact of (intentional) weight loss on cancer-related mechanisms still must be resolved. A promising novel mechanism linking obesity with endometrial cancer lies in the role of the immune system. The precise mechanisms linking obesity and immune evasion in endometrial cancer are complex and not fully understood which has prompted an increased interest in the interplay between immune cells, metabolism and endometrial tumorigenesis.

Donor:	World Cancer Research Fund International (GB)
Duration:	48 months
Funds for IARC:	€409 392.00
Funds for partners:	-
Total:	€409 392.00
Partners:	Imperial College London (GB), QIMR Berghofer Medical Research Institute (AU)

1.14 Project title: **Diabetes and Cancer Initiative: An international multi-cohort platform for investigating links between two global epidemics**

Type II diabetes mellitus (T2D) and cancer are two of the most significant causes of mortality and morbidity worldwide. It has been estimated that approximately 387 million individuals or 9% of individuals aged 25 years or over are diabetic while around 14 million new cases of cancer are diagnosed across worldwide each year. With a growing aging population across most regions of the world, it is expected that these figures will rise substantially in the coming decades. Interestingly, there is now emerging evidence from

both experimental and observational studies that cancer and T2D are linked and may share common etiologic pathways. Cancer and T2D are more frequently co-diagnosed in the same individual than would be expected by chance, even after adjustment for age, and there is epidemiological data indicating that diabetics have increased risk of developing a number of common malignancies including liver, pancreatic, endometrial, colorectal, postmenopausal breast, and bladder cancers. Evidence is less conclusive for other cancers such as those of the esophagus, kidney, and thyroid gland and for leukemia; however, few individual studies have been of sufficient size to investigate these tumour types with sufficient precision. Further, a critical, and as of yet, unanswered question, is whether the T2D-cancer association is primarily due to shared risk factors (obesity, diet, aging, sedentary lifestyle), or whether T2D itself, and the specific metabolic derangements that characterize T2D (e.g. hyperinsulinemia and hyperglycemia) increase risk of certain cancer types. There is also limited data on the impact of T2D on survival among cancer patients, and whether diabetes treatments can modulate cancer development and clinical course. To acquire the scientific knowledge needed to develop specific public health and clinical guidelines, substantial advances in the scientific evidence regarding the diabetes-cancer link are now required. The aims of our research programme are to address these knowledge gaps and to provide robust and definitive evidence on the role of diabetes in cancer development. This will be achieved by assembling the largest pooled cohort study conducted to date on diabetes and cancer comprising approximately 4 million individuals that will make it possible to stratify the analyses of the diabetes and cancer association by combinations of shared risk factors and investigate temporality of the diabetes and cancer relationship.

Donor:	Institut National du Cancer (FR)
Duration:	36 months
Funds for IARC:	€196 641.00
Funds for partner:	€107 136.00
Total:	€303 777.00
Partner :	Institut National de la Santé et de la Recherche Médicale (FR)

2. Prior approval for projects in collaboration with the private sector

There are no projects to be considered for prior approval this year.

3. 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.

Early Detection, Prevention, and Infections Branch (EPR)

3.1 Project title: **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**

Initially WHO recommended a three-dose schedule to be delivered over a six-month period for HPV vaccination irrespective of age. A multi-centre cluster randomised study supported by the Bill and Melinda Gates Foundation (BMGF) was initiated in India in 2009 to evaluate whether two-doses of quadrivalent

HPV vaccine (Gardasil™) administered over a six-month period to girls aged 10–18 years could be as effective as three doses in preventing persistent HPV infection and cervical neoplasia. The study aimed to recruit 20 000 unmarried girls aged 10–18 years and randomly allocate them to receive either two doses on days 1 and 180 (n = 10 000) or three doses (n = 10 000) on days 1, 60 and 180 of quadrivalent HPV vaccine. Recruitment and vaccination of the eligible girls was initiated in September 2009 and continued satisfactorily until April 2010, with more than 95% of the invited girls participating in the study, when the Indian authorities suspended further vaccination of subjects in all HPV vaccination trials in India due to certain events related to HPV vaccination outside our trial. The abrupt suspension of vaccination lead to the creation of multiple dose cohorts – three dose recipients, two dose recipients and a single dose recipients. Yearly follow up of all the participants is ongoing to estimate the protection offered by a single dose against persistent HPV infection and cervical precancers and cancers and compare the single dose vaccine efficacy to that of two and three doses. This study has already been instrumental in driving policies related to HPV vaccination.

Donor:	Bill & Melinda Gates Foundation (US)
Duration:	63 months
Funds for IARC:	€2 822 235.50 (US$ 3 416 750.00)
Funds for partners:	€3 493 980.00 (US$ 4 230 000.00)
Total:	€6 316 215.50 (US$ 7 646 750.00)
Partners:	Tata Memorial Centre Rural Cancer Project, Nargis Dutt Memorial Cancer Hospital (IN), Tata Memorial Center (IN), Jehangir Clinical Development Centre (IN), Christian Fellowship Community Health Centre (IN), Gujarat Cancer & Research Institute (IN), All India Institute of Medical Sciences (IN), India Institute of Public Health of Hyderabad (IN), Cancer Foundation of India (IN), Sikkim Manipal University/STNM Hospital (IN), Civil Hospital Aizawl (IN), Rajiv Gandhi Centre for Biotechnology (IN).

Evidence Synthesis and Classification Branch (ESC)

3.2 Project title: **IARC Monographs on the Identification of Carcinogenic Hazards to Humans - Y39 - Y43**

Since 1971, the IARC Monographs on the Identification of Carcinogenic Hazards to Humans has provided an evidence-based approach to identifying the preventable causes of human cancer. Organizations worldwide rely on the IARC Monographs as a trustworthy source of carcinogenicity evaluations in their efforts to control cancer. Agents evaluated by the Monographs encompass chemicals, physical and biological agents, complex mixtures, occupational exposure circumstances, and other exposures of everyday life. To date, 1021 agents have been evaluated, with 121 classified as “carcinogenic”, 89 as “probably carcinogenic”, and 315 as “possibly carcinogenic” to humans. Agents are selected for evaluation based on evidence of human exposure and of carcinogenicity, and public health importance. Monographs are developed by independent global experts without conflicts of interest. Each Monograph includes systematic reviews of the pertinent scientific literature covering three unique streams of evidence (cancer in humans, cancer in experimental animals, and mechanistic evidence). The overall evaluations indicate the strength of the evidence that an agent or exposure may be carcinogenic to humans. These evidence evaluations are guided by a recently modernized Preamble, which emphasizes scientific rigor and transparency of the systematic review, updates the supporting methods, increases emphasis on

mechanistic evidence, and advances an innovative method for integrating the three streams of evidence to produce robust overall classifications. The specific aims of this project are to: organize at least 10 Monographs meetings to evaluate candidate carcinogenic agents of high global relevance; convene expert Working Groups that are free of conflict of interest; further enhance methods and Web-based tools for the systematic search, screening, and evaluation of scientific data for carcinogenicity evaluations; advance the use of mechanistic data in carcinogen evaluations; widely disseminate the evaluation results; and engage in collaborations with national and international organizations to improve the science and practice of evaluating potential carcinogens. Important new initiatives in the proposed project period are to develop and apply tools for evaluating impacts of potential biases in human cancer studies; to refine and systematize the mechanistic evidence review according to key characteristics of carcinogens, incorporating novel scientific findings (i.e. from new approach methods in toxicology and molecular epidemiology); and to improve approaches for carcinogenic hazard and risk communications.

Donor:	National Institutes of Health - National Cancer Institute (US)
Duration:	60 months
Funds for IARC:	€4 155 603.87 (US$ 4 941 265.00)
Funds for partner:	n/a
Total:	€4 155 603.87 (US$ 4 941 265.00)
Partner:	n/a

4. 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 agreement, interest income amounting to €221.18 was apportioned to the below grant in 2021.

Grant No.	Project	Donor	Interest (in euros)
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	221.18