International Agency for Research on Cancer

World Health Organization

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Auditorium

REQUEST FOR SUPPORT FROM THE GOVERNING COUNCIL SPECIAL FUND

1.   An inter-disciplinary research approach is embedded within the IARC Medium-Term Strategy (2016–2020), with close integration of laboratory sciences, biostatistics, bioinformatics and epidemiology. This strategy requires high quality laboratories and availability of core items of state-of-the-art scientific equipment. It also requires support to research platforms for epidemiological research.

2.   Two pieces of equipment have been identified as necessary: a) to support DNA extraction in the IARC Biobank; and b) to support the analysis of metabolomics data in the Biomarkers Group. Covering the cost of new equipment on the regular budget has not been feasible in recent years and obtaining designated funds through competitive grant applications is difficult given the limited number of such opportunities open to the Agency as an international organization.

3.   The Agency has developed a unique collaborative project with the National Cancer Center, Republic of Korea (NCC) to investigate the prevention of gastric cancer by *Helicobacter pylori* (*H. pylori*) eradication in a randomized clinical trial (entitled HELPER). This project also provides a unique set of data and associated biospecimens. The project has been mainly funded by the NCC to date. The project is now reaching a critical phase and resources are requested from the Governing Council Special Fund (GCSF) to complement the support from the NCC.

4.   The Director would like to request the Governing Council (GC), at its 61st session in May 2019, to provide an allocation of €300 000 from the GCSF for the purchase of the equipment described below and €200 000 for the investment in the HELPER study. The proposed investment is first submitted to the Scientific Council (SC) for its consideration.

5.   The SC is requested to advise the Director and the GC on the proposed request to use funds from the GCSF to purchase the two pieces of scientific equipment mentioned and to complete the recruitment in the HELPER study.

A.   Purchase of scientific equipment

Equipment for the DNA extraction platform

6.   The IARC Biobank is a key integrated unit supporting the Agency's mission of coordinating and conducting research on cancer prevention by housing biospecimens from large cohort studies, and when necessary processing and re-distributing the collected material and/or associated data.

7.   The IARC Biobank now stores over six million biological samples from studies conducted in collaboration with or coordinated by IARC scientists. In addition, the Biobank provides storage space for studies conducted in low- and middle-income countries where optimal conditions for medium- to long-term sample storage are lacking, and to store duplicate samples.

8.   It is growing in size according to the research needs of the Agency, and at a predictable annual rate of just over 50 000 samples. Over the last two years with resources of the GCSF (request presented to the GC in 2016 [see Document SC/52/9]), a major investment has been made with the acquisition of -80C freezers (x12); LN2 tanks (x5), -40C freezers (x3) and automated LN2 tank (x1). These equipment purchases are expected to address current and future needs until the move to the Nouveau Centre.

9.   The IARC Biobank also processes upwards of 100 000 samples for many different studies per year. The process may vary from simple retrieval of samples, to that of pairing with matched controls, DNA extraction, and quality control for checking integrity of nucleic acids prior to shipping.

10.   The IARC Biobank performs on average DNA extractions from 4000–6000 samples per year with two automated DNA extraction systems. However, these systems purchased in 2008 and 2012 will cease to be supported by the manufacturer as of 1 January 2019, putting at risk the whole DNA extraction activity. Thus the current requirement is to replace the two ageing automated, high-throughput DNA extraction systems, with a single new system.

11.   Further to the above request, a gel imager is needed for routine verification of DNA integrity in agarose gels. It will complement a current gel imager servicing two communal laboratory areas located on separate floors, and will reduce risks of contamination during transfer of gels across different laboratory spaces and floors.

12.   The annual maintenance costs of the requested equipment will be integrated into the IARC regular budget as well as from extrabudgetary sources and invoicing for the Biobank services.

Software and databases for metabolomics

13.   Metabolic profiles are useful probes to explore biochemical mechanisms leading to cancer and to identify novel biomarkers of disease risk in intervention studies or large cohort studies. A strong platform with high-throughput based on mass spectrometry technology has been established at IARC and several tens of thousands blood and urine samples have been successfully analysed over the last five years.

14. The highly complex data collected in metabolomic experiments require sophisticated software and large spectral databases for metabolite annotation and data interpretation. A bioinformatician was recruited in 2018 in the Biomarkers Group (BMA) to support the analysis of metabolomic data generated on the BMA platform.

15. Various open access software tools and proprietary software developed by the mass spectrometry vendors are extensively used by BMA to support the analysis of metabolomic data. However, major progress has been made over the last five years in the development of bioinformatic tools and there is a need today to upgrade tools currently used on the platform. This will be essential for the IARC platform, to conduct state-of-the-art metabolomic studies in an increasingly competitive field of research.

16. Biomarker discovery experiments conducted at IARC through metabolomics largely used a single high-end high-resolution mass spectrometer (Agilent Technologies QTOF 6550), with an instrument-specific data processing pipeline. A second high-resolution mass spectrometer (ThermoFisher Scientific Q-Exactive) was purchased in 2015. However, it currently lacks the software (Compound Discoverer) to support high throughput processing of metabolomic data that has been developed by the manufacturer since 2015. This software is needed today to analyse a growing number of samples.

17. In addition to the acquisition of this new piece of software, upgrading the existing software for metabolomics is also needed. This applies to the Agilent Technology QTOF high-resolution mass spectrometer (MassHunter, PCDL Manager, METLIN Metabolomics Database and Library, SIMCA-P) and to two low-resolution mass spectrometers (SCIEX QTRAP 5500, Triple Quad 4500) purchased between 2011 and 2015. A change in the quantification tools currently used (MultiQuant) to a new cross-instrument platform (SCIEX OS), which features new algorithms that make data processing more efficient, is expected to increase laboratory productivity.

18. Purchase of the following software is therefore needed to help with current bottlenecks in metabolomic data analysis:

   a) Compound Discoverer software (ThermoFisher Scientific) for building custom metabolomic data processing workflows and assist in compound identification, one of the biggest challenges in metabolomics.

   b) Upgrade for several software items and databases currently used for the analysis of metabolomic data on mass spectrometers.

B.   Investment in the HELPER study

19. Gastric cancer causes almost 800 000 deaths per year and *H. pylori* is a major risk factor. However evidence is still limited as to the effect on gastric cancer of eradication of *H. pylori* with antimicrobial therapy. In response, a large randomized controlled clinical trial (HELPER) is being conducted in Korea in collaboration between the Prevention and Implementation Group within the IARC Section of Early Detection and Prevention (EDP/PRI) and the NCC.

20. HELPER has been taking place within the National Cancer Screening Program (NCSP) since 2014 in 12 designated major university hospitals and seven local divisions of the Korean Association of Health Promotion (KAHP) across Korea. The recruitment target is 11 000 people

with randomization of 5000 *H. pylori* positive participants (1:1 male to female ratio) to quadruple *H. pylori* treatment or identical placebo pills.

21.   As of October 2018, 8429 participants have been enrolled and 3763 were randomized. The recruitment is expected to be completed in 2019. Biennial follow-up is underway in the context of the NCSP and anticipated to run for 10 years after the end of recruitment. The study outcome is the incidence of gastric cancer, which in the context of the NCSP is usually early stage and has excellent survival. A Data Safety Monitoring Board (DSMB) has been set up in 2014 to safeguard the interests of study participants and to ensure the scientific validity of the study.

22.   The total funding from NCC amounts to US$ 2.4 million from 2014 to 2018. A further funding application to NCC for 2019 is submitted but not yet approved, with NCC investigators anticipating that the funding may be provided during the first half of 2019.

23.   During the study, IARC participated in the design and development of the study, has conducted multiple monitoring visits, coordinated the organization of the DSMB, and facilitated discussion with the Korean Ministry of Health and Welfare and other institutions such as KAHP, the Korean National Health Insurance Service, and the National Research Foundation of Korea seeking their potential support of the study.

24.   Despite the NCC's invaluable support the recruitment is extremely challenging and will not be completed by the end of 2018 as expected. The study has also been challenged by decreased prevalence of *H. pylori* infection and lower number of male participants. To overcome the imbalanced male to female ratio, male participants are being recruited successfully from an additional seven divisions of the KAHP, but this has incurred increased costs and slowed progress.

25.   Based on 2018 recruitment statistics, it is estimated reaching the recruitment target will take another year, to the end of 2019 while additional funding from the NCC, if confirmed, is likely to only cover six months of that period.

26.   This is a unique study which will have a major impact in guiding international policy for gastric cancer prevention. Specifically, the trial will be important to strengthen the evidence base on the impact and feasibility of *H. pylori* eradication for reduction in gastric cancer, an outstanding question of global importance for public health. Furthermore, HELPER will address potential adverse effects of the *H. pylori* eradication treatment, in addition to identifying other factors associated with gastric cancer development, which need consideration before initiating population-based *H. pylori* eradication programmes.

27.   Important ancillary studies are foreseen using the database and biospecimens collected within the study. Examples of these studies include but are not limited to investigate impact of eradication on gastric microbiota, factors related to development of gastric cancer precursors, and cost-effectiveness of population based *H. pylori* screening and treatment as a gastric cancer prevention strategy.

28.   As a consequence the Agency is requesting €200 000 from the GCSF to finance six additional months of operation of the HELPER study in 2019. Half of the requested fund would be required to keep the local research staff working at the 12 participating centres while the remaining fund will cover research activities, operational costs, and monitoring visits.

Requested budget

	Approximate cost (€)
Equipment for the DNA extraction platform	
High-throughput DNA extraction system	224 000
Gel imager	20 000
Sub-total	244 000
Software and databases for metabolomics	
Compound Discoverer software	20 500
Software upgrades	35 500
Sub-total	56 000
Investment in the HELPER study	
Staff cost for participating centres	100 000
Research activities and operational costs for participating centres	55 000
Materials and equipment cost	15 000
Monitoring visits	30 000
Sub-total	200 000
Total requested budget	**500 000**