International Agency for Research on Cancer

World Health Organization

Governing Council **GC/61/18**
Sixty-first Session 09/05/2019

Lyon, 16–17 May 2019
Auditorium

ADMISSION OF A NEW PARTICIPATING STATE

Hungary

1. The Director has the honour to inform the Governing Council that the Government of Hungary has applied to be admitted as a Participating State in the International Agency for Research on Cancer. This application was communicated in a letter dated 17 April 2019 and addressed to the Director-General of the World Health Organization (Appendix 1).

2. The Director-General transmitted this application to all Participating States by Note Verbale dated 8 May 2019 and informed them that it would be considered by the Governing Council in accordance with Rule 50 of the Rules of Procedure of the Governing Council. Note is taken of the date of delivery of the letter of application in relation to the time-limit stated in Rule 50.

3. The documents in relation to the application of the Government of Hungary were sent for review to the members of the Governing Council Subcommittee on the Admission of New Participating States, who met by teleconference on 2 May 2019, and will report to the Sixty-first Session of the Governing Council.

4. A report on cancer research activities by the Government of Hungary is also appended (Appendix 2).

Appendix 1

MINISTRY OF HUMAN CAPACITIES

1346-1/2019/EGPOL

Dr Tedros Adhanom Ghebreyesus
Director General

World Health Organization
Avenue Appia 20
CH-1211 Geneva 27

Switzerland

Budapest, „17" April 2019

Subject: Application for Admission of Hungary as a Participating State in the International Agency for Research on Cancer of the World Health Organization

Dear Director General,

On behalf of the Government of Hungary, the Ministry of Human Capacities formally requests admission as a Participating State in the International Agency for Research on Cancer (IARC), with immediate effect.

As per Articles III and XII of the Statute of IARC, please find attached our application for admission to the Agency, including a brief description of the cancer research and control activities in Hungary. I would be grateful if these documents could be forwarded to the IARC Governing Council before its next session to be held in Lyon on 16-18 May 2019.

The Ministry of Human Capacities, on behalf of the Government of Hungary hereby undertakes to observe and apply the provisions established in the IARC Statute, Rules and Regulations, including assuming the financial commitment associated with being a Participating State of the Agency, as assessed by its Governing Council.

The Ministry of Human Capacities, on behalf of the Government of Hungary, awaits processing of this application, and is looking forward to becoming a Participating State of IARC as soon as possible and to contributing effectively to the scientific and technical work of the Agency. Our understanding is that, on admission, Hungary would have full voting rights as from the first year of its participation.

Any further clarifications on this matter should be addressed to the State Secretariat for Health of the Ministry of Human Capacities of Hungary (address: H-1051 Budapest, Akadémia u. 3.) I would like to inform you as well that a copy of this letter has already been sent to Dr Christopher P. Wild, Director of IARC.

Yours sincerely,

Prof. Dr. Ildikó Horváth
Minister of State for Health

Enclosure: Summary of cancer research and control activities in Hungary

Appendix 2

Summary information for the attention of the Subcommittee on the Admission of new IARC Participating States

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1. A description of the current cancer research community, including relevant expertise in the areas of IARC activities

Cancer research in Hungary is organized around the National Institute of Oncology (NIO), which has been the epidemiological, organizational, methodological, treatment, research and training center of Hungarian oncology for more than half a century now. Set up in a similar way as National Cancer Centers elsewhere, it is the only comprehensive cancer center in Hungary and in neighboring countries. The institute is highly recognized for its work and bases its approach firmly on professional excellence and the quality of its human resources.

The Institute is at the center of cancer research in the country and partners with many academic institutions in their epidemiological, biological, statistical and clinical research. The partners are from the academic field, such as the Semmelweis University, Budapest, Eötvös Loránd University (ELTE), Budapest, University of Debrecen, University of Pécs, University of Rijeka, University of Szeged and others, such as the National Institute of Environmental Health, Budapest and the National Korányi Institute of Pulmonology and Tuberculosis, Budapest. Further important players are the Hungarian Central Statistical Office and National Cancer Registry.

Hungarian research is active in areas of cancer surveillance, health economic assessments, epidemiological research and research on the etiology of cancer. A lot of work is being carried out around screening for cervical, breast and colorectal cancer, but also for head and neck cancer. Work focuses more and more on biomarkers in screening technologies, and Hungary can be considered as a pioneer in the application of immunochemical testing for colorectal cancer. Studies are also underway to evaluate the cost-effectiveness of merging HPV vaccination programs with cervical cancer screening programmes in Hungary. Hungarian scientists have also built up a significant expertise in health impact assessment, as evidenced by a recent analysis of the novel smoke-free policy in Hungary.

In addition, internationally recognized molecular oncology research has been performed in Hungary for a long time. In Hungary the main research priorities are the following:

- Centralized epidemiological research (based on the National Cancer Registry) and biobank structure;
- Basic research on the molecular mechanisms of tumor formation and progression;
- Translational research conducted using the methods of functional genomics, proteomics and metabolomics as well as the harmonization of said research with basic and clinical research in order to develop new targeted and immune-therapeutic methods;
- Research on the mechanisms of resistance to applied therapies and the development of more effective therapeutic methods preventing therapy resistance;
- Setting up molecular diagnostic methods predicting and showing the effectiveness of therapies and treatments (surgical, radio- and chemo-) for personalized therapy;
- Developing tumor markers assisting in early detection as well as cost-effective, sensitive procedures suitable for detecting these markers for more effective treatment;
- Research activity aiming at cancer prevention;
- Developing new screening methods;
- Molecular genetic screening of hereditary tumors (genetic tests for familial cancers)

In order to achieve the above mentioned objectives, the NIO has recently proposed the following strategy:

-Prevention of tumor development:

- Assessment of genetic risk factors
- Tumor screening and early detection

-Design of molecular diagnosis and prognostics of tumors. Using genetic markers in the differential diagnosis of tumors Molecular staging

-Prognostic tumor markers

-Prediction of tumor therapy sensitivity, designing individual treatment regimen (Pharmacogenomics):

- Uncovering the molecular basis of drug sensitivity
- Uncovering the molecular basis of radio sensitivity
- Dosimetry of biological radio sensitivity

-Examination and usage of the molecular basis of immunotherapy (melanoma, head and neck cancers)

-The molecular basis of immunotherapy

-The identification of new anti-cancer therapeutic targets

In order to achieve the above mentioned goals the establishment of a national tumors bank and the genomics analysis of tumor samples is needed, which would enable the establishment of a Hungarian Oncogenomics Database. In order to establish the genomic database of characteristic to the Hungarian population the following strategic objectives are proposed:

1. Creating the necessary conditions for the development of tumorbanks at every Hungarian oncology center.
2. Developing the standard operating system (SOP) which ensures the operation of tumorbanks and their quality assurance.
3. Connecting the clinical and genomic database of cancer patients by the development of an IT network.
4. Developing the algorithms for new diagnostic and therapeutic procedures.

-Oncoproteomics/oncometabolomics:

In cancer as a result of acquired and – in rarer cases – inherited genetic mutations the expression and structure of proteins encoded by the specific genes can change. The structural changes of said proteins often lead to functional changes. The altered protein expression and the profile losses / gains quasi reprogram the biological function of the cells.

Mapping is essential to the identification of such proteins as new therapeutic targets. These proteins are playing a major role in carcinogenesis, tumors progression and the resistance mechanisms of currently used therapies. The analysis of protein expression as well as functional proteomic studies therefore have an essential role in the development of modern therapeutic methods. Priority should therefore be given to research on tissue samples and cellular systems, which targets the mechanistic analysis of cancer cell behavior.

Suggested areas to be emphasized:

The mapping of protein expression profile of tumor samples and the information gained are hypothesis driven mechanistic studies that allow the identification of new therapeutic targets. These include the following:

1. Different posttranslational protein analysis studies which affect/regulate signaling processes. In this case the control of protein functions of redox reactions have a key role besides kinome analysis. These redox reactions are the "upstream" regulators of phosphorylation pathways and are of key importance in significant oncological signaling pathways.
2. Metabolic analysis can be traced back to the over or under functioning of certain protein functions thus giving real clinical potential of identifying possible targets.
3. Mechanistic chemical/biochemical/enzymological analysis that are focused on the structural/molecular reasons for altered protein function thus facilitating/controlling the omic/analytical measurements and developing drugs to inhibit the identified target proteins.
4. Development of methods promoting proteomic and metabolomic analyses. All of the above mentioned areas are of particular importance in the case of cancers with poor prognosis and aggressive cancers, where targeted or immune therapy methods are not yet available or are limited. These include the following cancer types:
   a, Pancreatic cancer
   b, Breast cancer
   c, Melanoma
   d, Lung cancer
   e, Colorectal cancers

All of above clearly evidences a vibrant research community rooted in a solid research infrastructure that has many areas of mutual interest with IARC.

2. Details of the presence of a national cancer institute

As outlined above, the National Institute of Oncology plays a pivotal role in the research landscape of Hungary. It fosters collaborations into epidemiological studies, biological and clinical research and trains cancer researchers in various disciplines. It was set up in 1952, and spans a wide variety of research streams. The National Cancer Registry also operates within the Institute and collects cancer incidence and mortality data from all over the country. The Institute coordinates the Hungarian Oncology Network, which constitutes of 19 county oncology centers and four regional centers and also encompasses medical universities.

The NIO collaborates with several international organizations such as the Organization of European Cancer Institutes (OECI), the Union for International Cancer Control (UICC), the European Association for Cancer Research (EACR), the International Prevention Research Institute (iPRI), and the World Health Organization to name a few.

The National Institute of Oncology has also been participating in many International projects of the European Union, such as the EurocanPlatform consortium (2011-2016). The EurocanPlatform project was one of the largest European cancer research consortiums. The EC funded project brought together 28 European cancer institutions and organizations; NIO being the only partner from the Central and Eastern European region.

Another initiative that NIO took part in (2013-2016) as a WP leader was the BencCan project The

general objective of the BenchCan project was to benchmark comprehensive cancer care and yielded best practice examples in a way that contributes to improving the quality of interdisciplinary patient treatment. Another international research consortium that NIO participated in is the MAGICBULLET (2015-2018) that covers fields of tumor biology, biochemistry, pharmacology, synthetic chemistry, medicinal chemistry, spectroscopy, conformational analysis, and computational chemistry.

In addition, there are several currently running EU projects and joint actions NIO participates in either as a WP leader, WP co-leader or as a member. It includes the following: CHRODIS PLUS JOINT ACTION – Implementing Good Practices for Chronic Diseases (2017-2020); INTENT – Using Guidelines and Benchmarking to Trigger Social Entrepreneurship Solutions Towards Better Patient-centered Cancer Care in Central Europe (2017-2020); Joint Action on Rare Cancers (JARC) (2016-2019); ERN EURACAN – European Reference Networks – Rare Adult Solid Cancers (2017-2021); TRANSCAN-2 – Aligning National/regional Translational Cancer Research Programs and activities (2015-2019).

3. A description of cancer research funding in the public sectors

Research funding in Hungary comes essentially from governmental sources. One of the most important is the National Research, Development and Innovation Office (NRDI Office) that aims to establish a coordinated, predictable and sustainable system for research funding in which, through supporting excellent scientific research and promoting innovation, Hungary can ensure its research, development and innovation resources to be utilized not only in a legitimate but also an expedient manner, to increase Hungary's global competitiveness and foster its most fruitful integration in the European Research Area (ERA).

Established in 1986, the mission of the Hungarian Scientific Research Fund (OTKA) is to provide support to outstanding discovery oriented (basic) research in all fields of science carried out in Hungarian institutes. A similar funding structure is maintained in the new NKFIH domain complemented with several new funding schemes. In addition to institutional funding for higher education institutions, there are three main sources of RDI funding that are allocated on a competitive basis. One important source is the Research and Technological Innovation Fund. Another important source of funding is the various Operational Programs (OPs) co-financed by the EU Structural Funds. In the new programming period 2014-2020, it is planned that, out of nine OPs, three will specifically address STI. Five ministries (i.e., the ministries for National Economy, National Development and Innovation, Human Capacities, Public Administration and Justice as well as Rural Development) will be responsible for implementing the Operational Programs.

Finally, the National Health Insurance Fund of Hungary, created in 1993, is the public organization that currently controls the management of health care in Hungary, ensures the

education, training and examination of leaders and officers of the health insurance sector, and funds related research.

Funding in Hungary is allocated on a competitive basis and through a peer review system.

4. Information on a national cancer control plan

The epidemiological cancer burden of Hungary is among the highest in Europe. A considerable part of this statistics is however related to precise disease related administration mechanisms operating in Hungary.

The first National Cancer Control Program (NCPP) was set up in 1993 (and presented at the WHO meeting in Canada). The Hungarian data on cancer patterns and trends provided the basis for evaluating priorities for cancer control. These priorities determined also the priorities of the NCCP:

1. Primary prevention - Health Education, Oncology related programs on TV, Development of new education programs for the medical and paramedical staff.
2. Secondary prevention - Improvement of the screening system of breast, colorectal, cervix and head and neck tumors, Promotion of research (related to early detection)
3. Treatment - Establishment of treatment protocols
4. Establishment of a National Cancer Registries
5. Rehabilitation

The plan was first updated in 2006, and entails the following main elements: Cancer registration, primary prevention (reducing tobacco use, stimulating physical activity, curbing alcohol consumption, avoiding excessive sun exposure, enhancing awareness of occupational and environmental factors), secondary prevention with breast, colorectal, cervical and head and neck cancer screening, and general and palliative care.

As a directive of the Ministry of Human Capacities, the NCCP was most recently updated in 2018 by professionals at the NIO and a complex action plan was also developed addressing the most important challenges. The overreaching aim is to reduce cancer mortality by 10% in Hungary by 2030. The National Cancer Registry has been collecting data on incidence of cancers since 2000 and covers 100% of the population – hospitals are required by law to report cancer-related data to the National Cancer Registry quarterly.

Mammography-based breast cancer screening has a long tradition in Hungary and started as early as the late 1960s. Following the evaluation of pilot programs for mammography screening, a nationwide, organized population based breast cancer screening program was announced in 2001 and started in January 2002. Women aged between 45 and 65 years old were invited for participating in the breast cancer screening program.

Opportunistic cervical cancer screening started in Hungary during the 1970s. After the socialist system collapsed in 1990, Hungary initiated a new pilot program for the early detection of

cervical cancer. This program was financed by the World Bank. After three decades of opportunistic cervical cancer screening activities, an organized, nationwide cervical cancer screening was introduced in Hungary in July 2003 for women aged between 25 and 65 years.

In Hungary, there were several pilot programs for colorectal cancer screening at various points in time. In 1997–1998, the first Hungarian colorectal cancer screening program was piloted in a well-defined administrative area of the Capital, Budapest, with support from the World Bank. The second colorectal cancer screening pilot was organized in a small city of Ajka, and the surrounding area in 2003–2004. Later other small scale pilot programs were organized in different Hungarian cities and finally, in 2015, another pilot for colorectal cancer screening pilot program was initiated, this time financed from European Union. These pilot programs used immunochemical fecal occult blood test (FOBT) for the early detection of fecal blood. Following the evaluation of this pilot program, Hungarian health policy leaders committed to the introduction of a nationwide colorectal cancer screening program.

5. The potential for the Participating State to contribute to the research priorities of IARC, as described in the Agency's Medium-Term Strategy;

There is research expertise relevant to many of the research priorities of IARC. In particular:

Describing the occurrence of cancer: As outlined above, the National Cancer Registry of Hungary, which is maintained by the NIO, is a central element for cancer surveillance in the country. As such it can contribute to the cancer surveillance activities of the Agency, including Globocan, the Global Cancer Observatory, and the Childhood Cancer Registry.

Understanding the causes of cancer: IARC has collaborated with many partners including the National Institute of Environmental Health, Budapest, to corroborate a role of HPV in lung cancer. In collaboration with the HELENA (Healthy Lifestyle in Europe by Nutrition in Adolescence) study, IARC and researchers of the University of Pecs and others worked on the influence of parental socio-economic status on diet quality of European adolescents, and investigated usual energy and macronutrient intakes in 2-9-year-old European children. Scientists at the University of Debrecen have investigated DNA methylation characteristics of primary melanomas with distinct biological behavior in collaboration with IARC researchers. Researchers from the National Institute of Environmental Health, Budapest, have worked on rare variants of large effect in BRCA2 and CHEK2 affect risk of lung cancer and the effect of occupational exposures on lung cancer susceptibility.

Evaluating interventions and their implementation: As outlined earlier on, Hungarian scientists have been involved in implementing and assessing various cancer screening programs, including colorectal cancer, breast cancer, head and neck cancer and cervical cancer.

6. Evidence of current scientific and technical exchange with IARC.

- Dr Peter Rudnai from the National Institute of Environmental Health, Budapest, Hungary, is together with IARC one of many partners in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium, a large consortium to study head and neck cancer. INHANCE was established in 2004, based on the collaboration of research groups leading large molecular epidemiology studies of head & neck cancer that are on-going or have been recently completed. When taken collectively, questionnaire data on over 26,000 cases & 34,000 controls, and biological samples from a majority of the study population would be available. These studies have been conducted in various regions of the world.
- Dr Peter Rudnai participates equally in the International Lung Cancer Consortium (ILCCO), which is an international group of lung cancer researchers, established in 2004 with the aim of sharing comparable data from ongoing lung cancer case-control and cohort studies. Questionnaire data from a total of 26000 case-control pairs, and the biological samples from the majority of the subjects would be available. These studies are from different geographical areas and ethnicities. The overall objectives are to achieve greater power, especially for subgroup analyses, reduce duplication of research effort, replicate novel findings, and afford substantial cost savings through large collaborative efforts.
- Dr Peter Rudnai works closely with IARC scientists on exposure–response analyses of asbestos and lung cancer subtypes in a pooled analysis of case–control studies
- Prof Edith Olah from the National Institute of Oncology, Budapest, is involved in the A Transcriptome-Wide Association Study Among 97,898 Women to Identify Candidate Susceptibility Genes for Epithelial Ovarian Cancer Risk.
- Several Hungarian scientists, namely Dr. Regina Heidinger-Felso, from the University of Pécs, Dr. Viktoria A Kovacs from the National Institute of Pharmacy and Nutrition, Dr. Eva Martos from the Hungarian Society of Sports Medicine and Dr. Dénes Molnár from the University of Pécs are partners in the NCD Risk Factor Collaboration (NCD-RisC) together with many other scientists, including IARC. NCD-RisC is a network of health scientists around the world that provides rigorous and timely data on risk factors for non-communicable diseases (NCDs) for 200 countries and territories. The group works closely with the World Health Organisation (WHO), through the WHO Collaborating Centre on NCD Surveillance and Epidemiology at Imperial College London. NCD-RisC pools high-quality population-based data using advanced statistical methods, designed specifically for analyzing NCD risk factors. The Collaboration currently has data from over 2,545 population-based surveys from 193 countries since 1957, with nearly 129 million participants whose risk factor levels have been measured.

- Dr. Dénes Molnár from the University of Pécs collaborates with IARC on many studies into dietary patterns, Mediterranean diet, vitamin, calcium folate intake, metabolic syndrome and inflammation profile in overweight or obese adolescents in Europe (overall 15 co-authored papers in the last six years)
- Together with researches from IARC, Dr. Edit Bardi from the Semmelweis University, Budapest, is partner in the *PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies*, which is a consortium of 16 European institutions in 11 countries, funded by the 7th Framework Program of the EC, to carry out research studies into late effects of treatment for cancer, to establish guidelines for follow-up, and to disseminate the results and provide training and workshops for stakeholders.
- Dr Péter Hegyi from the University of Szeged is involved in collaborations with IARC on genome-wide analyses to identify new susceptibility loci for pancreatic cancer.

7. Joint publications in the last 5 years.

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