International Agency for Research on Cancer

World Health Organization

Scientific Council **SC/49/10**
Forty-ninth Session 14/12/2012

Lyon, 30 January–1 February 2013
Auditorium

FUTURE DIRECTION OF THE IARC BIOBANK

1. The IARC Biobank is a key resource supporting the Agency's mission of coordinating and conducting research on human cancer. This document describes the current state of development of the Biobank and the future plans, including the opportunities linked to the proposed new IARC building ("Nouveau Centre" project, see document SC/49/11). The Scientific Council is asked to provide advice to the Director on these areas, particularly in light of the Governing Council consideration of the new building project at its next session.

1) Introduction

2. Advances in laboratory sciences permit interactions between genes, environment, lifestyle and health to be investigated. Modern analytical methods enable applications to large biospecimen collections from epidemiological studies, thus making biobanks a cornerstone of population-based and clinical studies.

3. In this context, there are often advantages to collating biospecimens across collections and for individual biobanks to collaborate by pooling resources. The success of such collaboration will depend on the quality of biospecimen processing and storage, the type and format of clinical and demographic data collected with the samples, and the level of interoperability of the biobanks' processes.

4. Differing collection, processing and storage protocols can significantly alter biological specimen quality and consistency, which can in turn influence analytical outcomes and the ability to reproduce and compare results. Thus it is important that principles of best practice are applied at all levels of biospecimen management, from pre-acquisition phases to post-acquisition, processing and archiving. Equally important is the documentation of the applied protocols, compliance with the protocols and the management of the different sample databases.

5. In responding to these challenges, IARC aims to:

i) develop and maintain a Biobank that stores biospecimens of diverse origins and types, from different study designs, in the best possible conditions;

ii) ensure the effective management of data associated with the samples to facilitate linkage to associated databases;

iii) utilize appropriate technology in a state-of-the-art environment, equipped with automated systems;

iv) adhere to international standards and apply best practice principles with a sound quality control program;

v) play a leading role in the development of international standards and guidelines for biobanking, particularly in low-resource regions.

6. The potential construction of a new IARC building provides an exceptional opportunity for planning an expanded Biobank equipped with state-of-the-art technology and designed to respond adequately to the current and future demands in this area.

2) Current position

7. The IARC Biobank is managed as part of the Laboratory Services and Biobank (LSB) Group, which is within the Office of the Director.

8. Prior to 2011, the Agency did not have an integrated Biobank, but rather a biological resource centre that stored a diverse range of individual collections of biospecimens from different IARC research Groups, managed by the Groups using different types of databases.

9. Since 2011, following the formation of the LSB Group under the leadership of Dr Mendy, the strategy has been to a centralize biobank activities, incorporating the heterogeneous sample collections housed within IARC under one platform. This presents a considerable challenge in terms of the concept and resources but is a necessary part of the vision to maximize the value of IARC sample collections for the international cancer research community.

10. The LSB Group consists of 13 staff members (11 full-time and two part-time) with the costs of four full-time staff members covered by extra-budgetary resources obtained by cost recovery through internal and external collaborators using LSB services. It should be noted that the LSB staff also provide core laboratory service support to the Agency scientists.The Biobank Steering Committee (BSC) and IARC Ethics Committee (IEC) provide advice on strategy and direction and on ethics respectively.

11. The main Biobank-related activities of the LSB Group are:

i) to maintain a centralized facility for storage of biospecimens in a safe and secure environment;

ii) to facilitate collaborative projects with the international cancer research community through an appropriate access policy;

iii) to utilize appropriate technologies for sample management and pre-analytical sample processing;

iv) to provide technical advice to scientists in-house and externally on best practice in biobanking.

2.1 Biospecimen collections

12. The Biobank currently contains 5-6 million biospecimens obtained from population and diseased-based studies conducted worldwide. This total comprises a number of major collections (see list below) and over 20 smaller studies. The cataloguing of the biospecimens is ongoing (see section 2.2) and, with the assistance of principal investigators and research Groups, associated data are being collated that are not yet available in databases. In order to facilitate the process the plan is to categorize and prioritize the collections based on their potential research value.

13. Major collections include:

i) the EPIC study, conducted in 23 centres in 10 European countries (~3.8 million samples (at the beginning of the study);
ii) prevalence study of HPV in low- and middle-income countries (LMICs) (~113 000 samples);
iii) multicentre case-control studies on lung and kidney cancer in Russia (~45 000 samples);
iv) multicentre case-control studies on oral cancer conducted in Australia, Canada, Cuba, India, Ireland, Italy, Poland, Spain and Sudan (~23 000 samples);
v) multicentre case-control study on kidney cancer conducted in Eastern Europe (~35 000 samples);
vi) case-control study on alcohol-related cancers, genetic susceptibility to upper aero-digestive tract in Europe (~18 000 samples);
vii) worldwide case series studies on cervical cancer and human papillomavirus (~1 200 samples);
viii) prospective cohort study on digestive cancers from Iran (~300 000 samples).

14. In some instances the Biobank also acts as a custodian for the safe storage of biospecimen collections for colleagues from LMIC settings. The Biobank also stores cell lines from collaborative research studies, maintained as a back-up for local and international colleagues.

2.2 Cataloguing

15. Maintaining the extremely heterogeneous biospecimen collections of plasma, serum, buffy coat, red blood cells, urine, tissues and filter paper blood spots, kept in containers of diverse types and sizes, requires careful planning and management of storage space and conditions. In this regard, the recent focus has been the development of a reliable IT system and database program. Over the last five years an in-house Laboratory Information Management System entitled, Sample Management System for IARC Biobank (SAMI), was developed as a common tool to archive and manage sample location and associated data at IARC.

16. The inclusion of the Agency studies into the SAMI database started in 2011. To date, of the estimated ~1.5-2.0 million samples which constitute the major collections based at IARC (excluding EPIC samples which are stored in a separate database), 550 000 (~25%) have been inventoried (of which 350 000 have been uploaded to date, with another 200 000 in databases ready for migration into SAMI).

17. The cataloguing resulting from the introduction of SAMI has also allowed the restructuring of the storage facilities leading to a more efficient use of floor and freezer space and re-arrangement of samples. A centralized facility was created for the storage of ambient temperature samples (paraffin blocks, slides and filter paper dried blood spots) in a temperature and humidity controlled environment. The inventory and sample location verification process is on-going with the importation of data-files. Existing databases are also being prepared for migration into the common database.

2.3 Quality control

18. The Agency has recently invested in an automated freezer monitoring and alarm system to improve the cold storage facility and enhance sample preservation. The system connects over 60 freezers to an alarm system that allows real time monitoring and recording of temperature.

19. The quality control procedures in the pre-analytical platform were revised at the beginning of 2012, with the introduction of more stringent protocols to improve the quality of extracted DNA. The Agency is participating in a quality assurance scheme as part of the EC-financed SPIDIA (Standardization and improvement of generic pre-analytical tools and procedures for in-vitro diagnostics) project and will continue to participate in similar projects.

20. A quality control study was conducted on a total of 50 000 samples from the EPIC cohort with DNA extracted at IARC to identify pre-analytical factors affecting DNA quality and quantity for Genome Wide Association Studies. The study shows a wide variation in DNA yield between centres which was associated with the variation in collection techniques[1].

2.4 Financial Resources

21. The Biobank has been developing a financial model for sustainability by accurately calculating its costs, communicating this in a clear way to users and translating this into a process for recovery of operational costs (e.g. retrieval, processing and shipment of samples) linked to specific projects. The operational costs are now included in the budget of grant applications that require the Biobank participation.

22. The regular non-pay budget is used mainly for the cost of maintaining samples in the archives (liquid nitrogen, freezers, cataloguing, etc.). The major cost is liquid nitrogen, which amounts to €150 000 per year, with substantial additional research investments in freezers and racks to replace old equipment.

2.5 Access policy

23. IARC strives to ensure that the resources housed within the Biobank are being put to the best possible use. Within this context, the BSC in consultation with IARC scientists and external expertise, drafted guidelines detailing procedures by which outside researchers can apply for access to IARC samples (see Annex 1 below: IARC Policy on Access to Human Biological Materials). A catalogue of biospecimens is available at the Biobank web site and this, combined with the access policy should provide a basis for research proposals from new collaborators.

[1] Caboux E, Lallemand C, Ferro G, et al., PLoS One. 2012;7(7):e39821. Epub 2012 Jul 13.

24. Under the access policy, IARC Principal Investigators (PI's) will: review the requests and decide whether they conform with the principle of 'best possible use' and with the relevant access policies and statutes set up by the study and IARC; provide advice on ethics review; where applicable, obtain approval from the local recruiting centres for access to samples; provide the relevant anonymized biospecimen annotations and maintain records of requests for access, their outcome and reason(s) for denial, if appropriate.

25. The LSB Group will facilitate the sharing of biospecimens by: managing the material transfer agreement (MTA); archiving all relevant documentation relating to access; providing the requesting institute with detailed quotes; organizing sample retrieval, processing and the shipment of biospecimens; archiving the six-monthly progress report forms submitted by requesting institutes and monitoring the projects until completion.

3) Current and future directions

26. IARC plays a leading role as the coordinating centre for many international projects. It is likely that such activities will increase because of the growing international collaborative efforts to compare data obtained in different settings and the need for combined analyses for large-scale genetic and biomarker studies. More generally, the call for international, independent scientific expertise in all aspects of biobanking will increase and the Agency is well-placed to provide leadership in this area.

27. This section presents the specific contributions the Agency can make to biobanking both through support to IARC staff and in relation to development of this scientific discipline internationally. A description of some of the infrastructure developments to underpin these contributions, notably in relation to the new building project is also included.

3.1 Support to IARC scientists and external collaborators

28. The LSB Group will continue to provide the necessary support to ensure efficient management of the biospecimens in the IARC Biobank. Key priorities of the Agency's biobanking activities are to: ensure biospecimens are kept under optimal conditions; provide accurate information on sample availability and quality; ensure that associated data are transferred with the samples and to monitor the progress of research projects.

29. An additional role of the LSB Group is to provide technical advice to IARC research Groups to ensure uniformity of procedures and sample quality (see below). Infrastructure development is being considered in parallel with the strategic directions of the Biobank and sample database; sample security and quality assurance are the main focus.

3.1.1 Sample database:

30. The current sample management database, SAMI, is supported by an integrated IT system and enables users to upload, monitor and trace movements of samples stored in the Biobank. The original version of the SAMI program provided a structure for importation of basic information on the origin of the biospecimens and sample location. The program has been upgraded to deal with the heterogeneity of the Biobank samples and to provide information on associated datasets and documentation related to ethics issues.

31. With the development of a sample deposition form to collect standard information on study participants and sample quality, and the definition of a 'minimum dataset' (MDS) containing information on study, collection, ethics, biospecimen and preservation methods, etc., the program will undergo further expansion.

32. The collection of uniform data will facilitate the future usage and pooling of biospecimens for joint studies. The IARC MDS will be based on existing quality control tools such MIABIS (Minimum Information about BIobank data Sharing) and BRISQ (Biospecimen Reporting for Improved Study Quality). The SAMI database is being supported by two staff members from Genetic Cancer Susceptibility (GCS) and Information Technology Services (ITS) Groups. However due to the increase in maintenance tasks and the magnitude of the work needed for upgrading and expanding the program and making it accessible as a web-based tool, these demands will grow.

3.1.2 Sample security:

33. Maintaining samples in a stable and secure environment is an important priority of the Biobank. The current system of storing sample aliquots in the same storage equipment does not provide adequate safety for the samples. In future, sample aliquots will be stored in two separate archives (liquid nitrogen and -80°C freezers). Aliquots that are not likely to be used in the short-term will be stored in the ultra-low temperature storage facilities as a back-up, thus maintaining the long-term integrity of the sample fractions for future use.

3.1.3 Quality assurance:

34. Historically the Biobank has not been implicated as a matter of course at the time of study development and therefore in the pre-acquisition and acquisition stages of biospecimen processing. In the future it is planned for LSB to have more input in the planning of new studies, providing advice on collection procedures, processing, transportation and best practices for data collection, thus ensuring that best practice is observed throughout the sample acquisition phases. Tools and mechanisms will thus be in place to collect information on sample quality, from the point of acquisition to transportation to IARC.

35. Whilst sample collection and processing covers specific areas in biobanking (SOPs have already been developed to manage these processes), archiving and documentation are much broader involving all Biobank aspects, from sample reception to MTAs, shipment procedures and SOPs. The on-going revision of methodologies will reflect the requirements for quality assurance in each of these areas, e.g. the introduction of a sample deposition form, aiming at collecting standard information and MDS on study participants and sample quality (see 3.1.1 above).

3.2 Participation in international biobanking initiatives

36. IARC will continue to play a leading role in developing international biobanking guidelines and protocols. In particular, the IARC Green Book 'Common Minimum Technical Standards and Protocols for Biological Resource Centres'[2] published in 2007, will be revised as part of the newly awarded grant[3] (see below). The Agency will continue to participate in international networks

[2] http://www.iarc.fr/en/publications/pdfs-online/wrk/wrk2/index.php
[3] http://ec.europa.eu/research/infrastructures/index_en.cfm?pg=ri_projects_fp7

such as the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI)[4] and the EuroCanPlatform[5]. Membership of these organizations will enhance IARC's continued collaboration across the European community.

37. **BBMRI** is a EU-sponsored project to establish a pan-European bioresource infrastructure, through the creation of a network of new and existing biobanks, with common resources and technologies. The aim is to improve the quality and efficacy of European research in the life sciences, especially in biomedical research. **BBMRI-European Research Infrastructure Consortium (ERIC)** is the legal framework of BBMRI. The project will promote the integration of biomolecular resources and the development of common SOPs to improve access to the collections of biobanks, biomolecular resources and/or data. IARC has been engaged in the process of the BBMRI-ERIC application in order to explore how to be able to participate in this legal entity whilst not jeopardizing its own international status.

38. **The BBMRI-large prospective cohorts (BBMRI-LPC)** is a new EU-FP7 funded project, which aims to build a network connecting the established large scale epidemiological studies and associated biobanks. IARC is playing a leadership role in the overall project and will participate in work packages dealing with the improvement of the infrastructure for transnational access to the samples and data (including EPIC samples) and with the expansion of the European biobanking community to provide expertise and training for emerging countries' biobanks. As mentioned above, one of the work packages will also include the revision of the IARC Green Book regarding biobanking protocols.

39. **EuroCanPlatform** is another EU-funded FP7 project, which aims to create a European-wide infrastructure for translational cancer research. One biobanking work package (WP 10-Biobank) is devoted to using and building upon previous biobanking experience to identify and suggest solutions to stimulate cooperation and sharing of samples. Developing the IARC access policy is timely, as it provides the mechanism for sharing the Agency's resources with partners in these consortiums.

3.3 Support to biobanking in LMICs

40. The tools and methodologies used to develop Biobank infrastructures and population cohorts are limited in resource constrained settings but interest in conducting cancer research using such approaches in these regions is increasing. In response, the Agency is proposing to work with national and international partners to provide guidance and support in the development of biobanking procedures tailored to the needs of LMICs. The proposed international network will be coordinated by IARC and will aim to provide LMICs with solutions for establishing sustainable infrastructures that have already been tested and optimized in a variety of different settings. The network will bring together biobank personnel, medical researchers, biologists/oncologists, pathologists, health practitioners, public health and cancer registry personnel from LMICs.

[4] http://www.bbmri.eu/
[5] http://eurocanplatform.eu/

41. To avoid duplication of efforts, organizations who are active in supporting excellence in biobanking and cohort building in LMICs will be invited to be members of the network, including: the NCI Centre for Global Health (NCI-CGH)[6] and Biorepositories and Biospecimen Research Branch (BBRB)[7]; AORTIC (African Society for Research on Cancer and Training)[8]; ISBER (International Society of Biorepository and Environmental Biobanking)[9] and ESBB (European, Middle Eastern and African Society for Biopreservation and Biobanking)[10].

42. IARC is considering leading the network and providing:

- a platform for LMIC partners to collaborate with regional and international partners;
- access to international state-of-the art technologies and biobanking tools with the long-term aim of providing sustainable infrastructures for cohort building;
- possible access to the IARC Biobank to act as custodian of duplicate samples collected from network partners.

43. The project will be implemented in phases and will be dependent on generation of adequate resources among the partners.

44. The initial phase will comprise a situational analysis to assess the biobank infrastructure in the different LMICs to provide information on priority areas for support and to identify training needs. For each country or institution that wishes to join the network, the needs of the country or institution would eventually be mapped to a planned provision of tools, methodologies, education and support. This would result in an implementation and financing plan as well as specifications of the services, tools and support that IARC can provide.

45. An important goal of the network is to form a common platform to bring together countries and institutions to identify common research themes and develop grant applications to attract extra-budgetary funds. The available funds will support the network activities as part of its development programmes. In this regard, the network members will be well-placed to apply for funding through programmes such as the NIH's Human Heredity and Health in Africa (H3Africa) initiative for capacity building for bio-repositories in Africa (http://h3africa.org/).

46. The Agency is therefore currently considering how much emphasis to place on promoting biobanking best practices in LMICs; whether to assume a coordinating role in the proposed network; and to what extent the IARC Biobank should offer to act as custodian for samples from LMIC countries.

[6] http://www.cancer.gov/aboutnci/globalhealth
[7] http://biospecimens.cancer.gov/default.asp
[8] http://www.aortic2011.org/aortic/index.cfm/contact-us/
[9] http://www.isber.org/
[10] http://www.esbb.org/

3.4 Infrastructure: Biobank facilities

47. IARC biological resources are currently stored in multiple locations: on the different laboratory floors, in the basement of the tower building and in the Biological Resource Centre (BRC) building. This situation is far from ideal in relation to efforts towards establishing a centralized Biobank. The plans for a new Agency building offer an exciting opportunity to provide a modern Biobank fit for future purpose. Some of the principles being considered are described below.

48. The IARC Biobank will be an integral part of the new building designed for the long-term archiving of biological material. It will provide an appropriate environment for current needs, adaptable to the heterogeneity of the existing resources, with flexibility for application to a wide range of future scientific needs.

49. A major consideration is to ensure adequate floor space for future expansion and adequate cold storage facilities for existing collections, as well as the potential for automation. Currently the Biobank infrastructure consists of 46 large liquid nitrogen tanks plus 10 additional smaller ones as well as approximately 150 freezers.

50. The IARC Biobank should be located at one end of the building, with ground floor access to cater for expansion and easy access to services and liquid nitrogen supply. In terms of estimating the required footprint for the Biobank, the Agency has assessed the current space occupied in all locations (Tower and BRC buildings) by liquid nitrogen tanks and storage freezers as 750 m^2. Based on the projected growth in biospecimen collections (for example the Biobank has incorporated 300 000 additional specimens over the last 4-5 years) and the possibility of offering custodianship to collections from LMICs, the proposal is to increase the footprint by 20%. This modest increase reflects the major gains to be made by rationalizing storage space in an integrated and automated storage system which offers a far more economic use of space compared to conventional freezers.

51. Apart from the physical infrastructure, initial investments will be needed for cold storage equipment and in particular for an automated freezer system. Currently, most of the biospecimen retrieval is done manually from large liquid nitrogen tanks – a laborious, time-consuming and hazardous task; the physical nature of liquid nitrogen retrieval, involving the lifting of heavy racks, is onerous on staff well-being.

52. It is unlikely that retrieval from liquid nitrogen tanks will be automated in the near future, although the ergonomics of sample handling have been addressed in newer models of liquid nitrogen storage containers. Nevertheless, the plan for the Biobank is to move progressively towards a hybrid system of ultra-low temperature storage facilities (liquid nitrogen or -180°C freezers) and freezers (-80°C), with increased emphasis on a day-to-day basis on use of the latter. Duplicate samples will be stored in -80°C automated freezers, using liquid nitrogen or similar ultra-low temperature facilities as back-up, thus progressively increasing the level of retrieval from -80°C archives. Other benefits of automation include: easy access to samples, withdrawal performed under ultra-low temperature conditions which protects sample fractions from freeze-thaw degradation, and a safer work environment when compared to liquid nitrogen facilities.

53. Our strategy for introducing automation of freezer archives will be in two phases. In the initial phase, we will identify frequently used samples (or samples planned for future studies) in existing collection and transfer one aliquot (if they are in duplicate or more) from the stand-alone freezers into the automated archives; the remaining aliquots will be stored in the back-up facilities. Following the initial phase, aliquots of new sample collections will be separated and archived in the hybrid facilities thus providing a reliable alternative for biospecimen preservation.

54. The above strategy will not apply to older sample collections that are without barcode-labelling, as it will be difficult to program the biostore software to accommodate the samples. We will also maintain the existing 46 large liquid nitrogen tanks which contain the 3.9 million straws from the EPIC study, as this is the most efficient system to store the samples. However, the contents of the 10 small liquid nitrogen tanks will be moved into new larger tanks. This will both liberate floor space and remove the need for the manual liquid nitrogen filling required for the smaller tanks, which because of their size cannot be included in the pipeline for automatic filling. Additional large tanks (or equivalent capacity of ultra-low temperature freezers) will be required to accommodate the duplicate back-up samples, earmarked for long-term storage to complement the hybrid storage system. Investment in the hybrid storage system will require the acquisition of an automated modular archive system which is expandable.

4) Conclusion

55. The IARC Biobank has made significant progress during the last two years in:

- establishing an integrated system of catalogued biospecimens with links to associated data;
- defining the level and nature of support to IARC scientists and external collaborators;
- developing a sustainable financial model;
- developing an access policy as one critical step to ensuring that the best possible use of the biospecimen resources at the Agency;
- continuing participation in international biobanking initiatives.

56. The Agency is now seeking advice from the Scientific Council in terms of the overall direction and development in these core areas as well as on two new initiatives, notably the specification of the IARC Biobank as a core component of the proposed new building and the potential for the Agency to play a key role in supporting biobanking developments in LMICs.

Annex 1

International Agency for Research on Cancer (IARC) Policy on Access to Human Biological Materials

Purpose of the policy

The mission of IARC includes promoting cancer research on a global scale. Ensuring that biospecimens stored at IARC are being put to the best possible use is an important part of this mission. Within this context, the samples stored at IARC are available for research projects consistent with IARC's scientific goals and the IARC/WHO legal and ethical standard practices.

The purpose of this document is to set forth guidelines for a simple and clearly defined Access to Human Biological Samples policy, designed to i) promote the efficient use of the resources available at IARC in global cancer research and ii) promote the visibility of the ongoing research and usefulness of biological resources housed within IARC.

The current document provides information on:

1. How to contact IARC to request access to biospecimens;
2. The responsibilities of the requesting institute;
3. How the requests are reviewed by IARC;
4. The responsibilities of IARC.

The Laboratory Services and Biobank Group (LSB) is responsible for the management of biological resources including sample archiving, processing and redistribution, whilst the Biobank Steering Committee (BSC) oversees the biobanking activities.

1. How to contact IARC?

Requests for accessing biospecimens stored at IARC should be directed to the body responsible for the management of the biospecimen collection, defined as the principal custodian within this document. In most instances, the principal custodian is:

- The IARC scientist that has had the main responsibility for a research study, or to whom the responsibility for the research study was assigned (hereafter called principal investigator, or PI);
- The Steering Committee, for multi-centred studies when these are in place, for example the European Prospective Investigation into Cancer and nutrition (EPIC) study, the Steering Committee serves as the IARC contact;
- A Biobank Steering Committee (BSC) appointed contact for studies where there is no IARC PI.

A table listing the collections and IARC contacts is available at http://ibb.iarc.fr/collections/index.php

2. Responsibilities of the requesting institute

In submitting requests to access IARC samples:

- Requestors should be employees of a recognized academic or research organization and should provide information on their organization by completing a form available on the IARC Biobank web site (http://ibb.iarc.fr/);
- Provide a scientific protocol of the study and ethical approval for the use of the biological samples;
- Provide evidence that the researchers and institute scientific goals are consistent with IARC standards of research (http://intranet.iarc.fr/OfficeGuidelines/index.php);
- Provide plans for financial and human resources to undertake the proposed analyses (in the event that proposed analyses require the success of a grant application, authorization to use the biospecimens may be given, but samples will not be sent until the funding has been awarded);
- Accept and undertake research in the context of the ownership of samples and data under the conditions stipulated in the IARC material transfer agreement (MTA) (see template http://ibb.iarc.fr/standards/index.php);
- Pay all expenses for biospecimen retrieval, aliquoting and shipment;
- Provide plans for publication of the study results in peer reviewed journals within three years of reception of the samples (or clear justification for the requirement of a longer period);
- Complete a declaration using the form available from the Biobank web site every six months until samples have been used or destroyed or returned back to IARC (as is stipulated in the MTA). The form includes that the recipient has complied with the terms of the MTA and reported the outcome of the study (publication and project summary);
- Recipients found to be in breach of the MTA will be denied future access to the collections;
- Return to the principal custodian the raw data generated by the project six months after publication.

3. How does IARC review the requests?

The principal custodian will review the requests under the access policies and statutes set up by a particular study and the IARC Access policy.

The principle of best possible use can result in requests that are denied. Examples of valid reasons for denial are:

- The aims of the project are not in line with the medium and long-term objectives of IARC;
- The scientific quality of the project is considered inadequate;
- The available biospecimen volume is insufficient without compromising the future scientific value of the collection;
- The project overlaps with ongoing projects/analyses, meaning there would be unnecessary duplication of work and a waste of materials and other resources;

- There are ethical or legal incompatibilities with IARC's standard practices and the proposal (such as links with the tobacco industry, certain commercially orientated research or research goals inconsistent with the original specified purpose of the specimen collection).

To ensure the transparency of the application process and enable auditing of the use of the samples housed within IARC, the LSB is requested to keep records of all requests, their outcome and reasons for denial (as appropriate).

The BSC will appoint a Biobank Support & Development Working Group, on an ad hoc basis at the request of the principal custodian, which will comprise expertise in the major disciplines relevant to Biobank development and exploitation (epidemiology, statistics, IT, clinical sciences, laboratory sciences and the science of biobanking). The Working Group will be available to assist the principal custodian in handling requests and developing strategies for increasing the use of the resources as required.

IARC reserves the right to refuse any request without having to provide justification for decisions made.

4. Responsibilities of IARC

IARC'S interest is to ensure the optimal scientific use of biospecimen collection and associated data (biospecimen annotations) entrusted to us. In particular, the principal custodian is encouraged to identify new uses of the resources and to make cancer researchers globally aware of these possible new uses. The principal custodian is also responsible for ensuring the accuracy and quality of all original biospecimens and data collected.

Derived data or materials submitted to the collection may only be made available to other researchers with the permission of the originator.

If consent is withdrawn for issued samples, recipients will be informed of relevant sample numbers and asked to destroy any unused samples and certify that they have done so. Results obtained from samples that have already been used for research need not be destroyed.

The principal custodian will be responsible for:

- Supervising the IARC ethical submission process;
- When appropriate, obtaining approval from the Principal Investigators of local recruiting centres for access to samples for this use;
- Providing the relevant anonymized biospecimen annotations with the requested biospecimens;
- Maintaining records of requests for access, their outcome and reason(s) for denial, if appropriate;
- Providing requests for access information to LSB for central archiving.

The LSB Group will be responsible for:

- Obtaining the MTA signature;
- Archiving of all relevant documentations relating to access;
- Providing the requesting institute with detailed quotes for work to be performed;
- Organizing sample retrieval, processing and the shipment of biospecimens: samples will only be transferred to requestors named at the time of the original application or in subsequent applications and specified in the MTA; samples will not be shipped without a signed MTA;
- Sending invoices to the requesting institute. In some cases advance payment will be required before the shipment of the samples;
- Archiving the six-monthly progress report forms submitted by the requesting institute;
- Monitoring the projects until completion.