THE INTERNATIONAL BREAST CANCER STUDY GROUP

IBCSG Tissue Bank Policy

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1. Introduction

The IBCSG maintains a Tissue Bank of formalin-fixed, paraffin-embedded tissue specimens. It contains specimens from the majority of patients included in clinical trials conducted by the group since 1981. This high-quality material is being used for correlative studies that relate markers to clinical outcomes documented during the conduct and follow-up of our clinical trials. The purpose of such research is to improve our knowledge on the prevention, diagnosis and treatment of breast cancer.

This document outlines the current IBCSG policy and describes the organization of the IBCSG Tissue Bank.

2. Policy

IBCSG collects formalin-fixed, paraffin-embedded tissue from most patients included in IBCSG trials. The specimens are used for Central Pathology Review by the reference pathologist appointed for the trial, and for any translational research specified in the trial protocol. Central pathology review, which includes immunohistochemistry characterization is integral to the IBCSG Trials. From the formalin fixed paraffin embedded blocks transferred to the IBCSG. cores will be punched to construct Tissue Micro Arrays (TMA). All FFPE blocks, TMA blocks, or other derivatives thereof, will be logged in the IBCSG Pathology Material Tracking System and banked in the IBCSG Tissue Bank to have available for translational research. This high-quality material is kept for future research/ translational research that is not yet specified at the time of collection.

Collection, shipping, storage and research are done under strict observation of patients' rights and confidentiality.

The IBCSG Tissue Bank and the IBCSG Central Pathology Office are located at the European Institute of Oncology in Milan, Italy..

The material collected is, in principle, regarded as donated by the patients for research. There is no international consensus on the issue of ownership of material. IBCSG therefore has custodianship of the samples.

The material is used in research projects proposed by IBCSG investigators or scientists outside of IBCSG. Collaboration with commercial companies is not excluded, but no material will be sold for profit. All institutions who receive specimen samples for research projects must adhere to the same ethical standards as IBCSG.

In rare cases, intellectual property may arise from a research project. The intellectual property rights will remain with IBCSG and any financial gain will be reinvested in IBCSG research.

All material is kept for an indefinite length of time. No FFPE blocks are destroyed. Material is sent back to the pathologist if requested.

Should IBCSG decide to stop pursuing the IBCSG Tissue Bank, it would pass the Tissue Bank on to a non-profit research organization adhering to the same ethical standards, but would not sell it.

3. Governance

The IBCSG Tissue Bank is under the ultimate responsibility of the IBCSG Foundation Council.

The IBCSG Biological Projects Working Group (BPWG) serves as an advisory committee to the Executive Committee on the scientific value and the priority of research projects and the proper use of the material.

The IBCSG Executive Committee decides on all submitted projects and involves the Foundation Council where appropriate.

Any research project using material from the IBCSG Tissue Bank must be approved by the IBCSG Ethics Committee.

The IBCSG Director supervises the Central Pathology Office.

The Principal Investigator of any research facility to which tissue material, or any derivatives thereof, is shipped for a specific project signs a written agreement with IBCSG stating the use of the material and the rules applicable for surplus material. Material which can be used for further projects must be shipped back to the IBCSG Tissue Bank.

All publications arising from such projects will follow the IBCSG Guidelines for Presentation and Publication (Appendix 3)

4. Ethical considerations

IBCSG is the custodian of all patients' tissue material. As such, IBCSG will make optimal use of the material for research purposes, while guarding the patients' interests.

The protection of the patients' rights and safety are the basis for the maintenance and use of the IBCSG Tissue Bank. The collected tissue specimens are used according to the written consent obtained from the patient.

The Patient Information Sheet and Informed Consent (PIS/IC) are developed according to IBCSG standards and must be adapted to local laws and regulations (see Appendix 1, PIS/IC template).

The confidentiality of the patients is maintained by coding all material specimens with a unique patient identifier at the participating center, even before the material is provided to the IBCSG Tissue Bank... The patient identifier corresponds to the one used in the clinical database of the trial. All samples and derivatives thereof are being provided to researchers as anonymized, with a

Translational Research Identifier (TRI), a laboratory reference number. This TRI effectively inhibits the identification of patients and only permits the correlation with clinical data in the IBCSG database. All samples shipped from the IBCSG Central Pathology Office to a research facility is marked exclusively with this identifier and cannot be linked to the patient's name or origin by the recipient. Access to patient identification is restricted to personnel at the treating institution. Personnel of the IBCSG Coordinating Center, the Central Pathology Office, the Data Management Center and Statistical Center can link the specimen to the patient's data in the clinical database, but not to the patient's name (see also section 5).

The IBCSG Ethics Committee is in charge of judging the ethical implications of any research project involving tissue material. Only upon approval of this ethics committee will a project be pursued.

The institutional review board (IRB) and/or ethics committee (EC) responsible for the institution by which the patient was included in the trial will be asked for approval of any new research project with the patient's material. The prior positive decision of the IBCSG Ethics Committee will be distributed to the institutions. The decision of the IRB/EC will also cover patients who have died.

Re-consent of the individual patients for a new research project will not be sought, except if declared mandatory by the responsible ethics committee.

In case a patient revokes her prior consent for future use of her material, all paraffin embedded material will be sent back to her pathology institute, whereas derived material (RNA, DNA, etc.) will be destroyed. Ongoing research projects including material from such a patient will, however, continue to use the data derived from previous use of her material.

In case of incidental findings with immediate clinical relevance for the patient, her treating physician will be informed and will be in charge of contacting the patient based on local regulations.

In earlier trials, tissue material was collected without explicit patient consent for future unspecified research. Material from such patients is especially valuable due to the long-term follow-up available for them. Their material will be used in future research after having obtained the approval from the local IRB/EC for each project.

5. Organization and management

The IBCSG Executive Committee presides over the IBCSG Tissue Bank. The Director of the Central Pathology Office and the Translational Research Coordinator manage it. The IBCSG Tissue Bank Standard Operating Procedures regulate the work of IBCSG Central Pathology Office personnel.

The IBCSG Tissue Bank adequately stores the paraffin-embedded tissue specimens. A quality management system is set up for storage conditions.

All aspects of specimen collection, processing and distribution, as well as the details of the patients' consent, are stored in the Pathology Material Tracking System (PMTS), an informatics system maintained by the Programming Staff at the Data Management Center. The unique patient/trial identifier is the only key providing the link with the demographic and clinical data of the patient.

The institutions that have recruited patients into clinical trials maintain lists of patients and their unique IBCSG patient identifiers. This allows the randomizing institution to identify and contact a patient if necessary. IBCSG Tissue Bank personnel, Data Management Center personnel or Statistical Center personnel cannot identify or contact patients.

6. Technical and operational guidelines

All aspects related to the IBCSG Tissue Bank operations are supported by the PMTS, which is linked to other IBCSG informatics systems, ensuring reliable tracking of patient randomization and consent, specimen and data collection, processing, banking and dissemination. The IBCSG Tissue Bank Standard Operating Procedures regulate all these activities.

When a patient is randomized, the Central Pathology Office contacts the local pathologist and/or Data Manager and requests the material that is required per protocol for central pathology review and storage at the IBCSG Tissue Bank (Pathology Form, Pathology Reports, paraffin blocks/ representative H&E sections).

The samples sent for Central Pathology Review and further research are only marked with the IBCSG randomization number and pathology specimen number, ensuring that the privacy and confidentiality of the patient is protected. The tissue consent level of each patient can be tracked in the PMTS.

Blocks /sections are permanently banked in the IBCSG Tissue Bank, unless the submitting pathology institution has asked for some or all the material to be returned for medical or legal reasons or wish of the patient.

The paraffin-embedded blocks and glass slides are stored at temperatures below 27ºC / 80°F, in an area with pest and humidity control (1), without any identifiable patient information.

7. Translational Research projects

Research projects should be structured according to the checklist of project proposal (Appendix 2) and are submitted to the Translational Research Coordinator. The BPWG is put in charge of assessing the scientific aspects and the priority of each project, which includes assessment of originality, methodology, priority, feasibility. The number of samples needed is determined in collaboration with the Statistical Center. The tissue material is scarce and should be used in the best possible way. Therefore use of each block is carefully

assessed with respect to the amount of material to be allocated for a certain project.

Once the project description has approval from the BPWG, it is submitted to the Executive Committee for approval, which decides if the project should be submitted to the Scientific Committee and/or the Foundation Council. Every approved project will be submitted to the Ethics committee prior to initiation.

For approved projects, the principal investigator of the research facility which will examine the specimens allocated for the project will have to sign an agreement with IBCSG on confidentiality, data and material transfer, and collaboration with the Statistical Center in correlating biomolecular findings with clinical data.

Appendix 1: see the document Biological Material Collection PIS-IC.doc

Appendix 2: checklist of research proposal submitted to IBCSG

- applicant(s), institution(s)
- Title
- Abstract
- Starting date, duration
- Short rationale
- Short description of planned investigations, timelines
- Objectives, endpoints
- Patient selection (which trials, which subgroups of patients)
- Short descriptions of lab methods and involved labs
- Material needed
    - Tissue
    - Clinical information
- Use of leftover material after project completion
- Statistical considerations
- Ethical considerations
- Impact on patient
- Feedback to patient
- Budget
- Acceptance of regulations and conditions for applicants

Appendix 3: see the document IBCSG Guidelines for Publication and Presentations.doc

References:

1. . National Cancer Institute Best Practices for Biospecimen Resources, 2007 National Cancer Institute, United States Department of Health and Human services . http://biospecimens.cancer.gov/practices/default.asp

2. 2008 Best Practices for Repositories,*Collection, Storage, Retrieval and Distribution of Biological Materials for Research* International Society for Environmental and Biological Repositories (ISBER), USA. Published in CELL PRESERVATION TECHNOLOGY Volume 6, Number 1, 2008, Mary Ann Liebert, Inc., DOI: 10.1089/cpt.2008.9997

3. Brian R. Leyland-Jones et al. Recommendations for Collection and Handling of Specimens From Group Breast Cancer Clinical Trials , J Clin Oncol. 2008 December 1; 26(34): 5638–5644.