EUROPEAN COMMISSION

nuclear science and technology

Genetic pathways for the prediction of the effects of irradiation European Normal and Tumour Tissue Bank and Database

(GENEPI-ENTB)

Contract N° FIR1-CT2002-20213

Final report
(summary)

Work performed as part of the European Atomic Energy Community's research and training programme in the field of nuclear energy 1998-2002 (Fifth Framework Programme)
Generic research in radiological sciences

Directorate-General for Research
Euratom

2008

Project coordinator

C. Verfaillie, European Society for Therapeutic Radiology and Oncology (ESTRO) (BE)

Project partners

ESTRO (BE)

TUD Dresden (DE)

UZ GHB Leuven (BE)

MedLawConsult (NL)

GCI Northwood (UK) (till December 2004)

Fondation Jean Dausset – CEPH (FR)

Objectives

The European tissue bank and database GENEPI-ENTB is dedicated to research in radiation effects and in the genetic determinants of the variation in individual radiosensitivity. The primary aim of GENEPI-ENTB was to create a tissue bank linked to a detailed outcome database of a large cohort of patients receiving radiotherapy and the development of a lymphocyte tissue bank containing samples from a cohort of large kindred French families, equally linked to a database. For that reason it was planned to establish a central database providing links to existing decentral databases and tissue banks, enabling optimal utilisation and access to data and material. It was GENEPI-ENTB's aim to network fragmented research efforts in this way, to open up often dormant resources in comprehensive cancer centres for well-equipped laboratories with no access to clinical facilities (such as nuclear research centres), and to create a high-quality shared infrastructure for projects dedicated to radiation research.

From the start it was decided that the tissue bank would remain open for at least 20 years, thus providing an excellent resource for future genetic research in the field of health risks linked to occupational, environmental, and medical exposure at all dose levels.

To guarantee the quality of GENEPI-ENTB, dummy runs with modern statistical tools were planned to monitor the quality of this novel research infrastructure as well as the development of protocols for outcome assessment, tissue handling, and use and access of the infrastructure.

Another objective of GENEPI was to create a frame of reference for researchers who want to exchange tissue in the context of the GENEPI resource and to address the relevant ethical and legal issues to ensure that the project would be handled in compliance with all existing legislation and appropriate legal and ethical standards.

Brief descriptions of work performed and methods

The focus in the first two years of the project was on the development of common protocols and the identification of high-quality tissues obtained from radiotherapy (RT) patients in the framework of clinical trials in which both treatment data such as dose distributions and the radiation responses were carefully registered.

The original objective, a central tissue bank, needed to be abandoned early on in favour of the creation of a central database linking the distributed tissue banks and their respective databases. The GENEPI database contains an essential data-set for each of the decentrally stored tissues. Besides, it describes which additional data are available in distributed databases. The advantage of including already stored tissues from large clinical trials is that scientists investigating late radiation effects will not have to wait for several years until these effects show up.

As of the third year, prospective tissue collection was started. For this activity, prospective partners were invited to sign a contractual commitment to adhere to commonly agreed procedures and protocols. At the same time a system of online data assessment, continuous data validation and quality control was developed in order to maximise the potential usefulness of the resource.

Main achievements

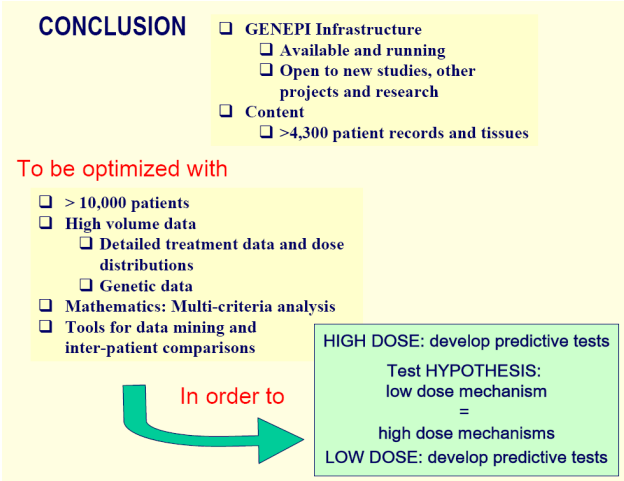
With 12 017 tissues from 6 790 individuals linked to solid outcome data stored, GENEPI is the largest infrastructure in this field worldwide: Two years after the launch of the project, GENEPI was already referred to as "the most comprehensive (tissue bank) in this regard" in a publication of the International Atomic Energy Agency reporting on "radiogenomics and the characterisation of molecular profiles that predict normal tissue and tumour radio-response" (West et al., IJROBP 2005).

Originally it was planned to include material and data from 3-4 000 patients within the project period of three years. The patients selected for enrolment in the GENEPI project were irradiated according to defined protocols to curative doses for breast cancer, head and neck cancer, lung, rectal cancer, and prostate cancer. GENEPI more than achieved its stated goals. The outcome of the project clearly demonstrates that a successful international collaboration to build up an urgently needed infrastructure, without direct benefits for the contributors other than participating in a collaborative effort pursuing shared research and professional interests, is possible. Beyond this, the strong motivation of the scientific partners for participating bears testimony to the fact that a joint initiative such as the GENEPI project can achieve excellent acceptance as a tool to improve the basis for research in the field of radiation effects. Part of the material included in GENEPI was buried or dormant in isolated centres, without any projects for further analyses. The obvious additional benefit that can be derived from documenting and pooling data stored in distributed databases and tissue banks lies in the power of numbers: numbers of patients that can be accrued and the associated robustness of the data and their statistical power, an essential prerequisite for research of any significance in the search for a genomic basis for the variability in individual radiosensitivity. None of the partners can reach in isolation the target numbers required for highly powerful analyses that will soon be available thanks to the GENEPI project. For this reason all partners clearly expressed their vision that, in view of the achieved results to date and the potential for future use, they wish to support the project further.

An inestimable plus value for the GENEPI tissues (DNA or lymphocytes and other normal and tumour tissues) obtained from radiotherapy (RT) patients is the database linked to it. For each tissue, treatment data, epidemiologic information, and outcome data are recorded. Moreover, the GENEPI database contains, submitted per patient, a minimum data-set that is in the public domain. This allows scientists to screen the suitability of the infrastructure for their research purposes prior to submitting an official application for access.

Exploitation and dissemination

The final aim of GENEPI is to more than triple the current number of samples to enable the selection of statistically relevant groups and even of highly stratified subgroups for analysis – briefly to keep all future avenues of research open. For this reason a new project was submitted to Euratom to ensure the quantitative and qualitative further development of the infrastructure till it reaches the level where it can match all present and future requirements of the research community. The grant application received very high scores from the evaluators. Should it nevertheless not be selected for funding, other avenues for reaching the objectives of the proposers will be explored.



The tissue bank opened to the research community, it is announced widely via its website, and communications at meetings and a number of excellent articles have been published on the database and tissue bank and research based on material from GENEPI.

So far two applications for the use of the GENEPI infrastructure were received. Any partnership agreement with research consortia will include a commitment to feed genetic data (SNPs, microarrays, etc.) derived from GENEPI tissues back into the GENEPI database. For this purpose new database functionalities will have to be developed.

Concrete examples of potential spin-offs of GENEPI-enabled research could include predictive assays for radiosensitivity grading, molecular modulation of radiation response, and tools for the improved radioprotection of individuals. Such innovations could be important contributors to cost-efficient health-care delivery. Beyond this, there may be realistic perspectives for commercial applications and exploitation underpinning the long-term financial sustainability of the infrastructure.

In this context it can be mentioned that pre-treatment gene-expression profiling by micro-arrays in tumours has already been demonstrated to have an important predictive value for the progression of disease (e.g. with regard to rapid metastatic spread), although studies specific to the outcome of radiotherapy are still lacking.