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New challenges in the biomedical science: biobanking problems and solutions

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Background. A huge progress has been recently made in the field of biomedical research and personalized medicine. Despite the advances of biobanking, significant limitations remain that are restricting the impact of researches. The major issues include the need to increase the quality and standardization of biospecimens and to maintain public trust. In general, it is named as harmonization of biobanking activities. **The purpose of this article** is to overview the current situation in biobanking issues and discuss about the possible solutions of these problems in Lithuania. The first steps in biobanking activities were made in the Institute of Oncology, Vilnius University (IOVU); several methods of DNA extraction from peripheral blood were tested and compared.

Materials and methods. During the experiment, four manual DNA extractions and one automated DNA purification method to determine the efficiency of each method in terms of the purity and yields of DNA extracted from blood samples were tested. DNA from patient's blood remaining after a routine blood test was purified.

Results. Two of the four manual extraction methods produced good yields of DNA (from 57 to 126 μg/ml), the other two were of poor quality (from 8 to 47 μg/ml). In the same samples automatically isolated DNA concentrations ranged from 15 to 95 μg/ml.

Conclusions. The first steps for biobanking activities, SOPs creation and process harmonization were made in IOVU. Finally, after appreciation of the general situation the main threats in Lithuania could be proposed. The general working plan and strategy for biobanking in Lithuania, according to international rules and national needs, must be applied.

Key words: biobanking, harmonization, SOPs, DNA extraction, DNA long-term storage

INTRODUCTION

A huge progress has been recently made in the field of biomedical research and personalized medicine. It was based on the identification of a variety of biomarkers and opportunity to apply the personalization for an individual patient in the disease prevention, diagnostics or treatment. The human genome sequencing has facilitated studying of various disorders like rare diseases or cancer and has opened great possibilities to the development of

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targeted drug therapies in the personalized medicine (1). In the medical definition used by the glossary of the National Institute of Health in the United States the personalized medicine is an emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease. The great medical progress has been influenced by the development of genomics, proteomics and other various -omics technological platforms and gain in bioinformatics, molecular-imaging, molecular diagnostics and drug development (2). Therefore, different biobanks, as the organised collections consisting of biological samples and associated clinical data, are increasingly established as a crucial base for medical research and further development of personalized medicine. In order to ensure the common understanding and practice in the implementation of the directives of the European Union (EU) related to biobanking, the European Commission (EC) has a vision to establish and link various biobanks together to the common European infrastructure (3).

Regarding these new scientific challenges in the world and Europe here is the need to establish the biobanking infrastructures and the common network in Lithuania with various important activities in creating of a governance and quality management model. After creation of such model the network of biobanks in Lithuania will operate according to the common standard operating procedures (SOP), joint quality control system according to the EU regulations and will have an integrated virtual data system. It is foreseen that the supported network of Lithuanian biobanks will be a significant contribution to the biomedical research and development of the European research area.

The purpose of this article is to overview the current situation in biobanking issues and discuss about the possible solutions of these problems in Lithuania.

Current situation in Lithuania

Today in Lithuania there is a great potential to perform the high technology and good quality biomedical research and to participate in the international research projects. In the new scientific valleys adequate and sufficient research infrastructures with new high technologies, equipment and human resources are concentrated. These valleys are like home for laboratory facilities of research institutes, pharmaceutical production facilities, private high-technology Research and Development centers (R&D), key academic training centers, "open access" labs and incubators. In addition, Government funds are allocated to construct new business incubators for biotechnology and start-ups by the end of 2013.

Therefore, for the modern biomedical research and biotechnological platforms the huge amount of the best quality biological material is needed. Biobank – it is a type of biorepository that stores various biological samples (usually human) and associated data for use in research. Today the biobanks in the world are modern infrastructures for different high technology researches. Currently in Lithuania only disease-based biorepositories or project-based biobanks exist in a few research institutions, university hospitals and clinics with an insufficient number of samples stored. As examples are the Cancer Tissue Biobank in the Institute of Oncology, Vilnius University (IOVU), the Hematological Patients Tissues Bank in the Vilnius University Hospital Santariskiu Clinics, the Great Pathological Material Archive in the National Centre of Pathology and the Dry Blood Samples Archive in the Centre for Medical Genetics.

However, there are no exact rules or legislation for the biobanking, integration and networking among these disease or project-based biobanks, there are no common SOPs for specimens operation and quality management, and an integrated virtual data base system is missing.

Bioethical and legislation problems

The majority of weaknesses described above are influenced by the fact that regulation of collecting, storing and distribution of biological resources in Lithuania is administered according to the Law of Bioethics created in 2000 with some corrections in 2008. It means that the Lithuanian legislation oriented to biobanking has not been fully created or adjusted according to the EU directives. The main challenges in this field of biobanking are related with bioethical problems, personal data protection and the collection, processing, storage and sharing of biological samples. It is known that the main advantage of biobanks is a quick and efficient access to collected human biological material and

associated clinical data. These possibilities increase competitiveness in medical research and reduce the time and attempt for achieving of scientific results that promote scientific progress (4). In the past decades there is an increasing interest for international collaboration of various biobanks in different fields named as harmonization of biobanks. The harmonization includes sample processing, data management and governance interlinking the ethical and legal aspects (5).

One of the main challenges in biobanking is to ensure an effective and ethical access to biological samples and associated clinical data. The most important question, discussed in the EU, is the promotion and implementation of general ethical principles in the biobanking: the concepts of donor's solidarity and altruism for common global public health. Trust between donors and researchers must be being built so that individuals would like to donate to biobanks (5). The solution of this problem requires an international collaboration in creation of the governance with high level privacy and an adequate access of samples. As an example, it could be the development of various training programmes for biotechnologists, IT specialists and members of ethics review and data regulatory boards as well (3).

Personal data protection problems

The other actual question, discussed in the papers, is rights and expectations of donors to determine the using of their biological material and data for the research purposes. The greatest problem regarding the donors is to ensure the security of their privacy (5). On the one hand, the benefit of biobanks is the support of biomedical research and medical progress. On the other hand, it is the securing and protection of donor's privacy and personal data (4).

So, a significant issue in biobanking is the protection of the donor's privacy. Different worries regarding biobanking and personal data protection are hardly discussed in the popular press and the professional literature. Described are assumptions about the possibilities of determining the presence of DNA from various individual biological samples, opportunities of personal identification using genetical data, posted in the virtual databases and using these data by the insurance companies or employers and other discussions concerning biobanking (6).

Thus, new challenges in the field of biobanking require the developing of a modern secure system that, on the one hand, protects the privacy, autonomy and other rights of donors, on the other hand, it could not be the retardation for the development of research.

Samples processing problems

As discussed previously, the general principle of biobanking is the harmonization of all procedures. Harmonization of biobanking operational procedures is the key element that enables different biobanks to exchange the biological material and associated clinical data. However, among various biobanks different SOPs of samples processing are implemented. Due to these reasons today the harmonization is still a more flexible approach aimed at ensuring the effective interchange of valid information and samples. However, to ensure more effective using of collected material, here is the demand to implement common standardization that implies precisely the same protocols and SOPs used by all biobanks (7).

Experience of DNA samples processing for biobanking purposes in IOVU

Today, in the modern world of science an increasing demand for samples stored in biobanks for different research purposes is observed. There is no doubt that samples stored in the biobank should be of high quality and meet the standards because, otherwise, they may be unused. Many molecular-genetic researches require high-quality of purified DNA. Due to these reasons all DNA samples stored in the biobanks must be of high quality: the appropriate concentration, purity and the degree of absorption.

Poor quality of the purified DNA long-term storage may begin to cause contamination with nucleases and degradation. DNA concentration and purity is highly dependent on the choice of the purification methodology, method, and the material from which DNA was purified.

There are a number of genomic DNA purification methods: in 1989 and 2001, J. Sambrook and co-authors (8, 9), other researchers (10) proposed protocols, later different commercial companies offered DNA purification kits using the columns and the magnetic particles, and finally automated DNA purification devices. As biobanks mainly use residual blood, it means blood samples after routine

blood tests, so it is very important to choose the most reliable method for DNA purification. The most reliable – it is primarily a qualitative way of purified DNA.

Each DNA purification method has its advantages and drawbacks in respect of the purified DNA quality and quantity, purification time and financial costs. DNA samples stored in the biobank raise extremely high quality requirements because it is not clear when this material will be used in the research. Good quality DNA is a prerequisite for achieving good results of the experiment (11), and polymerase chain reaction (PCR) or sequencing, where the poor quality of purified DNA and excess protein can inhibit the progress of the reaction (12).

MATERIALS AND METHODS

As described previously, there are wide varieties of different techniques, methods or protocols available for extraction and purification of DNA from the blood samples. Each method has its own advantages and disadvantages. In the Biobank of IOVU four manual DNA extractions and one automated DNA purification method to determine the efficiency of each method in the terms of the purity and amount of DNA extracted from blood samples were tested. Manually DNA was purified by organic extraction with the phenol-chloroform method; additionally 3-different sets of commercial kits were evaluated.

Blood specimens

10 peripheral blood samples, remaining after a routine blood test, were tested. For various diagnostical tests peripheral blood was taken down into 2–6 ml of a vacuum tube with EDTA. After diagnostical procedures the remaining amount of the 10 samples was divided into five tubes of 200 µl and stored at 4 °C for 10–12 hours or longer periods of time frozen at –20 °C.

DNA extraction

At first all samples were thawed to room temperature. Manually DNA was purified by the phenol chloroform method in a laboratory approved methodology, a set of commercial support and automated extraction according to manufacturer's recommendations and protocols. The DNA was eluted in 100 µl of DNA elution buffer.

Evaluation of extracted DNA

The purity of the extracted DNA by different methods was assessed using two different spectrophotometers and by calculating A260/A280 ratio for protein impurities according to the standard protocols recommended by the manufacturers. The yield of DNA was calculated from the A260 for clean DNA samples.

Statistical analysis

The extracted DNA concentration and purity average were calculated. The statistical analysis was performed using the Student's t-test for paired samples to compare the DNA yields obtained by various protocols. The differences were considered to be essential when P is less or equal to 0.05.

RESULTS

In the two of the four samples purified manually DNA concentrations and purity were good enough (from 57 to 126 µg/ml and from 1.66 to 1.86 m), the lack of quality of the other two was observed (from 8 to 47 µg/ml and from 1.55 to 1.82). In the same samples purified automatically DNA concentrations ranged from 15 to 95 µg/ml and the purity was from 1.78 to 1.88. The yields and the purity of DNA for each extraction method and averages are shown in Tables 1, 2.

Despite the lack of quality of purified samples statistically significant differences were detected between the extracted DNA concentration or purity using various extraction methods ($p < 0.05$). All methods, used in our experiment, could be applied for the biobanking needs. On the other hand, the phenol-chloroform method of DNA extraction generated higher quantities than using commercial DNA kits but differences were not statistically significant probably due to a small number of cases analyzed.

DISCUSSION

New possibilities for the biotechnological research, pharmaceutical companies, and medical sciences with the biobanking activities are opened. However, these activities bring new challenges for the biomedical society, scientists, and bioethical boards.

During the first year of initial works for biobanking activities in the new established Biobank

Table 1. Yield of DNA extracted by different purification techniques

Method / Samples	Yield of DNA, µg/ml, Photometer I, Photometer II										DNA average, µg/ml
	1	2	3	4	5	6	7	8	9	10	
Phenol-chloroform	60	120	120	100	100	120	60	100	100	100	98
	78	125	124	100	97	123	78	113	100	114	105
Kit No. 1	70	110	100	125	100	120	125	70	90	126	104
	57	118	107	125	88	114	122	70	85	122	101
Kit No. 2	30	30	30	40	30	30	30	30	20	30	30
	30	26	26	47	30	25	26	40	16	24	29
Kit No. 3	30	20	20	20	20	20	30	20	10	20	21
	32	26	22	26	24	26	32	23	8	21	24
Automated	60	80	60	30	60	20	80	20	60	90	56
	60	79	61	29	51	15	82	24	60	95	56

Table 2. Purity of DNA (A_{260}/A_{280}) extracted by different purification techniques

Method / Samples	Purity of DNA (A_{260}/A_{280}), Photometer I, Photometer II										DNA average, µg/ml
	1	2	3	4	5	6	7	8	9	10	
Phenol-chloroform	1.79	1.81	1.86	1.84	1.80	1.78	1.78	1.81	1.79	1.72	1.80
	1.78	1.82	1.79	1.79	1.82	1.80	1.81	1.83	1.79	1.75	1.80
Kit No. 1	1.66	1.70	1.76	1.85	1.75	1.73	1.77	1.76	1.75	1.78	1.75
	1.79	1.76	1.83	1.81	1.81	1.80	1.82	1.79	1.80	1.82	1.80
Kit No. 2	1.61	1.68	1.63	1.71	1.62	1.61	1.68	1.60	1.69	1.79	1.66
	1.76	1.78	1.75	1.71	1.69	1.71	1.79	1.79	1.73	1.82	1.75
Kit Nr. 3	1.55	1.56	1.56	1.61	1.61	1.58	1.61	1.59	1.71	1.78	1.62
	1.56	1.56	1.55	1.62	1.60	1.60	1.63	1.56	1.70	1.81	1.62
Automated	1.78	1.82	1.80	1.79	1.88	1.80	1.80	1.85	1.80	1.84	1.82
	1.83	1.84	1.84	1.81	1.88	1.81	1.80	1.87	1.82	1.83	1.83

at IOVU, experiments of the DNA extraction from blood samples were performed. According to the literature data, purification of DNA from patient's blood remaining after a routine blood test using the phenol-chloroform method is the right way to extract the DNA of good quality, but this method is toxic (13, 14) and requires a lot of manual work. During our experiment it was observed that the purity of the manual and automated purification DNA samples was similar, but the automated extraction was in loss of DNA quantity. We also found that the phenol-chloroform method of DNA extraction generated higher quantities than using commercial DNA kits.

According to our data we can say that from patient's blood, remaining after a routine blood test for biobanking needs, DNA can be effectively extracted with the phenol-chloroform method or some commercial compilations. When working with commercial DNA isolation kits prior to the acquisition it is necessary to test it on a variety of old blood samples. One of the basic principles in the biobanking activities are harmonization of various processes between different biobanks in the world. Testing, validation of various processes and SOPs creating are the basic requirements in good working biobanks (15, 16). This our experience could help other Lithuanian researchers in creating and validating of SOPs for DNA extraction.

Solutions of data protection problems

Not only harmonization of technical procedures has an impact on the biobanking activities. Other important question is the personal data protection. Various solutions for the personal data protection are discussed in the literature. One of the possibilities to highly protect personal data is using of new modern coding systems. In

the literature the new biobanking data protection methods that use a biotechnological tool to better protect the donor's privacy and associated data in a biobank are described. Securing and protection of donor's privacy and personal data could be warranted using modern informative technology solutions. Use of the modern, generated using high technologies biocodes (named Bio-PIN) could ensure that biospecimens and their associated data will be anonymous (6). Next solution or possibility is that the donors could participate anonymous in the biobanking activities; donation of biomaterial could be made in the way of altruism and free donation (17). Using this way, the donor does not require signing the informed consent. Moreover, after few decades the informed consent given several years ago cannot properly reflect the current situation in the point of view of new demand in biomedical research and developing various -omics technologies (4). Today the scientists could not expect what kind of the researches will be performed and what kind of biological material will be needed. So, the common principle could be applied for the biobanks – once given a general informed consent of patients, attending to the hospitals, to use the remaining biological material for various scientific purposes in the future.

Solution of bioethical problems

Since in Lithuania there are no law and legislation for the biobanking activities this field of research is still staying in retardation. This situation and scientific progress in the world need the revision of the Law of Bioethics in the new era of biotechnological investigations and progress. We hope that after implementing of a new Law of Bioethics there will be an opportunity to create new and integrate now existing disease-based biorepositories or project-based biobanks into the common network. This aim is foreseen to be achieved through the creation of a governance and quality management model for biobanking and networking: common legal rules adjusted to EU directives, SOPs and quality management of biobanks' activity, an integrated virtual database system.

Solution of bioethical problems is one of the primary tasks since in the field of biobanking they are very actual. One of the main challenges will be to ensure ethical, effective, and equitable access to banked data and samples. The solution of this problem will require international consensus guidance and collaboration to ensure equitable approaches to the governance of privacy and the development of training programmes for members of ethics review boards and other data regulatory bodies (5). Large scales of bioethical rules must be applied in the world and European biobanks. It is not expectations what the common rules and law for the whole world with various ethnical, religious and cultural traditions will be applied. However, general rules according to human rights must be implemented in the biobanking activities.

Opportunities

It should be obvious that support to the establishment of a network of biobanks will greatly increase the potential to perform the high technology and good quality biomedical research and to promote common international projects in the research area. Collection of samples according to the standardized EU methodology will give opportunities to join the International Network of Biobanks, to conduct joint investigations and to compare our results with other research teams. Here are great possibilities to incorporate into international biobanking networks like Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) (18), International Society for Biological and Environmental Repositories (ISBER) (19), European, Middle Eastern and African Society for Biopreservation and Biobanking (ESBB) (20) and others. After joining into the international network, there will be a possibility to exchange the biological material and related clinical information, to offer other institutions high quality samples for extended scientific research, and to apply for the EU Framework Programmes, HORIZON 2020.

Moreover, involvement of stakeholders from governmental institutions, non-governmental organizations and business partners, pharmaceutical and biotechnological enterprises which are potential data consumers in developing new drugs and diagnostics measures, the process of creation of a governance and quality management model for the network of biobanks will give the opportunity to achieve solutions based on social and economical needs and also to make consensus on different approaches to the problems that should be tackled.

In conclusion, the first steps for biobanking activities, SOPs creation and process harmonization were made in IOVU. Finally, after appreciation of the general situation the main threats in Lithuania could be proposed. The general working plan and strategy for biobanking in Lithuania, described and listed in various recommendations for biobanking (5), must be applied as follows:

- Establishment of standardized operating procedures governed by appropriate international quality management systems;
- Harmonization of quality management systems between biobanks and various networks;
- Continued education to improve technologies for preservation of biospecimens and data collection processes;
- Collaboration of multidisciplinary professionals for improving of the bioethical law according to international experience and national needs;
- Progress in information infrastructure to facilitate data sharing, implementation of new technical solutions for data management and protection of participant's privacy and data confidentiality;
- Trust making between researchers, business partners and society.

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NAUJI IŠŠŪKIAI BIOMEDICINOS MOKSLAMS: BIOBANKŲ PROBLEMOS IR SPRENDIMAI

Santrauka

Įvadas. Pastaraisiais metais, atliekant biomedicininius mokslinius tyrimus ir plėtojant individualizuotą mediciną, matomas ryškus progresas. Nors plečiant biobankus pasiekta pažanga, kyla įvairių problemų, apsunkinančių mokslinius tyrimus. Didžiausios problemos, su kuriomis susiduriama steigiant biobankus ir plėtojant jų veiklą įvairiose šalyse, yra standartizuotų procedūrų ir vienos kokybės kontrolės sistemos nebuvimas apdorojant ir saugant biologinius mėginius, visuomenės nepasitikėjimas šia veikla dėl nepakankamos informacijos. Tokius procesus galima pavadinti biobankų veiklos harmonizavimu. Šio straipsnio tikslas – apžvelgti esamą biobankų situaciją ir aptarti veiklos plėtojimo galimybes Lietuvoje. Parengiamieji darbai buvo atlikti Vilniaus universiteto Onkologijos institute: įvertinta ir palyginta keletas DNR gryninimo iš periferinio kraujo metodų.

Medžiaga ir metodai. Eksperimento metu vertinome keturis rankinius ir vieną automatizuotą DNR gryninimo metodus ir siekėme nustatyti kiekvieno metodo efektyvumą pagal išgrynintos DNR kiekį ir švarumą. DNR gryninta iš onkologinių pacientų kraujo, likusio po įprastinių diagnostinių kraujo tyrimų.

Rezultatai. Dviem iš keturių rankiniu būdu atliktų gryninimų atvejais DNR koncentracija buvo pakankamai gera (57–126 μg/ml), kitais dviem – nepakankama (8–47 μg/ml). Tų pačių mėginių automatizuotai grynintos DNR koncentracija svyravo nuo 15 iki 95 μg/ml.

Apibendrindami galime teigti, kad VUOI vykdomi parengiamieji biobankų steigimo bei jų veiklos darbai: rengiamos standartinės veiklos procedūros, harmonizuojami procesai. Išanalizavę ir įvertinę bendrą situaciją Lietuvoje, rekomenduojame sudaryti ir įdiegti biobankų veiklos plėtojimo strateginius planus atsižvelgiant į tarptautines rekomendacijas ir nacionalinius poreikius.

Raktažodžiai: biobankas, harmonizacija, SVP, DNR gryninimas, DNR ilgalaikis saugojimas