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Advances in Biobanking Practice Through Public and Private Collaborations

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FOREWORD 1

The present book addresses a significant gap in our collective knowledge on biobanking advancement through public-private partnerships. These partnerships are often alluded to in the peer-reviewed literature however one remains hard pressed to find and review a convincing, consistent body of evidence. The book moves quickly and effectively beyond a descriptive listing of the current landscape and sets as its core quest the aim of improvement. This improvement is multi-faceted: it can involve amongst others individual biobanks, collaborative projects, reference/national centers, qualitative standards, Intellectual Property (IP) issues, rights and obligations of stakeholders; all brought together for the common purpose of public and private benefit.

Over the past two decades the biobanking field has enjoyed a period of sustained investment, growth, wider scientific acceptance and development. Additionally, individual biobanks have benefited by support from very active, scientific community-driven societies, such as ISBER, the International Society for Biological and Environmental Repositories, and others. This has created a strong foundation for the regular exchange of experiences, the development of best practices and creation of educational tools with a global reach, especially as the biobanking field develops in Asia, Africa and south America. However, as the global financial crisis has developed into an enduring pressure for tighter cost control, expense justification and even cost retrieval, new operational models need to be considered for long-term sustainability in biobanking. This book investigates these alternative approaches which can operate in collaboration with the private sector yet without limiting their public benefit.

The editors have selected six distinct perspectives to provide a holistic approach in their subject. These are: Current practices; Quality management systems; Specimens quality; Rights and obligations of stakeholders; Collaboration models and Case studies. Sub-themes include the complementation and conflicts of different sectors and skill sets; the accreditation options and processes; the inherent trust in sample acquisition and processing, including biosafety. At the same time legal frameworks, different collaboration models and case studies are being brought together as a living corpus of evidence. It is indeed a very good collection of workable examples presented by some of the most respected scientific leaders in the field.

This book is an impressive and comprehensive study that moves beyond stereotypes that the biobanking field has often faced. It analyses why partnerships work and the future aspects that still need to be explored. Within the ISBER community there is the acute realization that private partners, commonly from the pharmaceutical industry, are often an essential component in addressing complex, healthcare related questions effectively and efficiently. The public –private partnerships have the potential to form a long-term, reliable infrastructure network enabling the discovery of new pharmaceutical agents, effective re-purposing of existing ones and preparedness in global health emergencies. I sincerely hope that more such examples will develop and strengthen in years to come, allaying public hesitation, and that a similar body of evidence will be developed in the not too distant future from our colleagues in Asia, Africa and south America.

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FOREWORD 2

When walking the long way in the development of new products and methods to be used for patient treatment or diagnosis, medical translational research needs to be able to exchange knowledge and biomaterials in the public-private domain. Collaboration in this area is often indispensable for the final innovation of patient care. Funding institutions understand this need and increasingly try to stimulate this important domain where many exciting and interesting opportunities can be found. At the same time, it is also a difficult area to work with biomaterials as it means yet another boundary where you need to learn to deal with new often stricter rules with respect to ethics and regulatory issues. Yet this is certainly not the only aspect important for a smooth cooperation, also the quality of the samples are very crucial. Especially where reproducibility is concerned which can be a show stopper easily and unexpectedly encountered. Certainly the moment after the research process where a developed method or product needs to be validated for its intended use. In this step, one has to rely on the quality of the routine diagnostic samples which might be collected under very different pre-analytical conditions as the samples that were used in the discovery phase. The infrastructure of the biobank becomes very important. It should reflect or better yet make use of the existing routine diagnostic pathways. In addition, the quality of the diagnostic sample is in need for improvement to facilitate new products and methods more efficiently.

Of course there is an array of ways how the public and private partners can collaborate. Therefore, the editors have invited and selected the experts in their fields with much care to write chapters on:

- The importance, benefits and unique results that are obtained from the public private partnerships,
- Theoretical collaboration models and good examples of practical solutions and tips,
- How quality can contribute to the collaboration,
- The influence on legislation and ethics,
- Concrete examples of public-private collaborations based on local infrastructure synergies.

This logical line is also chosen to set up the book to become a consistent and structured overview of the complex domain of public private partnership. It consists of six interesting chapters, where each chapter starts with an abstract of the content. The field is an exciting and dynamic one with many opportunities for scientists from the academic setting and companies to find common grounds to synergistically grow in win-win environments.

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PREFACE

The reflection on collaboration between public and private institutions in biobanking is crucial for making advances in this field.

Precision Medicine (PM), digitization and virtualization are quickly changing the biobanking landscape by asking for new models and concepts of synergies between public and private (or for profit) organizations.

However, this theme is currently under-analysis both in the literature and in scientific debates. The need for developing or improving collaborations between public and private institutions is recognized by several scholars but it still remains a niche topic in biobanking.

Furthermore, the reasons for developing public-private synergies (also called partnerships) are usually connected to biobank sustainability, on the public side, and to the acquisition of academic know how, on the private side.

This interpretation of the public-private-partnership (PPP) in biobanking seems to simplify the complexity of the issues related to public and private collaborations. It also seems to reduce the huge potentiality of promoting public-private synergies for biobanking advances and the related benefits for both public and private organizations working in this field.

Taking the above discussion into consideration, this ebook analyzes perspectives, methods and concrete ways to change the current models of collaboration between public and private organizations in order to improve biobanking practices.

The first chapter (Morente and colleagues) describes the state-of-the-art of public-private collaborations in biobanking on a global scale and it defines potential ways to improve these synergies. By highlighting that "the promotion of health" unconditionally should be the final goal of any partnership between public and private organization, Morente *et al*., list several criteria to reconsider the current theories of PPP in biobanking.

Innovative approaches to public-private collaborations in biobanking are suggested by Lawlor and colleagues (chapter two). After an extensive analysis of "old" and current strategies of liaison in this realm, Lawlor *et al*., recommend concrete models and methods of PPP to improve the biobanking practice.

The quality management system as a key aspect for public-private synergies in biobanking is the subject of chapter three. Bravo and colleagues extensively analyze the work of the technical committee "ISO T C 276 biotechnology" related to biotechnology standardization by focusing on biobanks and bioresources. The authors give a clear explanation of the role of ISO biotechnology standards to improve the quality of services for biobanks and to offer access to new markets for industries.

The description of quality standard criteria specifically tailored for tumor biobanks is provided by Bonizzi *et al*., (chapter four). The authors report the standard requirements to be followed for processing samples and data in daily practice. These criteria are not different for public or private "partners". High level of quality is demanded by each organization for using the samples stored in the biobanks, regardless of the public or private nature of the inquiring institutions.

The access conditions to biobanks is the theme analyzed in chapter five by Verlinden and colleagues. After a deep analysis of the general legal framework governing biobanks at national (Belgium), European and international levels, Verlinden *et al*., consider the access conditions to human biological samples and associated information.

Access conditions to samples and information stored in biobanks within the concrete model of the "HUB-BTB- 3CR" is the subject of chapter six. Di Donato *et al*., describe the HUB-BTB-3CR which is a centralized organization for managing sample requests. This model enables public and private researchers to directly access the biobanks which are part of the hub. Although tailored for organizations operating in France, this prototype of public-private collaborations could be used in other countries with modifications as per requirements.

Moving from the theory to the practice, this ebook suggests an accessible analysis of the main issues related to public-private partnerships in biobanking. It considers apparently conflicting concepts, such as academia, industry, profit and solidarity illustrating that they are not necessarily in contrast when trust, transparency and reciprocity are the basis of public-private collaborations in biobanking.

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CHAPTER 1

Public-Private Partnerships in Biobanking: Current Practices

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Abstract: Public-private partnerships (PPPs) and relationships are essential to expedite the resolution of the challenges currently facing Medicine. Biobanking is not an island within biomedical research as a whole, and public–private partnerships in biobanking must therefore be considered in the global context of biomedical research.

PPPs are certainly desirable, since they offer benefits to both sides, create win-win situations and are extremely advantageous for the whole society, but they have their own limitations and frontiers.

The current chapter tries to introduce the general aspects of current PPP practices in biobanking, keeping in mind that the main objective should be the promotion of health rather than the sustainability of biobanks or benefits for industry.

Compliance with applicable legislation, mutual trust, transparency and open dialogue are the key components of such partnerships.

Keywords: Biobank management, Biobanking, Public-private partnership, Translational research.

INTRODUCTION: THE CHALLENGE OF PERSONALISED MEDICINE

Biospecimen science is a young and evolving discipline that arose from the paradigm shift induced by the great biotechnological advances that took place in the last decades of the 20th century and by the accessibility and knowledge of the human genome and its progressive application to healthcare in Personalised Medicine [1, 2]. These changes are triggering, indeed, a revolution in the study and understanding of more complex and multi-factorial diseases such as cancer,

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diabetes, and cardiovascular or neurodegenerative processes. This increased knowledge of the pathogenic bases of complex diseases is not merely of academic value, but it also has practical value that enables improvements in their prevention, diagnosis, prognostic evaluation and therapeutic approaches. Developing and evaluating novel therapies and diagnostic products requires access to rigorously designed and well-structured collections of biospecimens, and this places biobanking infrastructures in a critical position for the discovery, development and implementation of new drugs and products [3].

PUBLIC-PRIVATE RELATIONSHIPS: A NON-HOMOGENEOUS MODEL

Not only the academia and health care sectors are involved in this challenge, but also the industry [4], although their objectives do not always coincide. There are many nuances, but it can be said that health promotion and disease control are true goals in both sectors, although they are approached from different angles.

Before continuing this discussion, it is important to note that 'private' and 'public' have different meanings in different cultures and social models. Indeed, both terms have specific and differentiated connotations in, for instance, the United States of America, Europe, East Asia or emerging countries. Not only do these concepts have different meanings, but the private and public domains in the health care systems and biomedical research, including infrastructures such as biobanks, have a different weight. In addition, we can say the same about Europe as a whole, and about specific European countries, especially when an essential component of the discussion refers to health care systems. Domestic differences in public health care systems, in the development of funding of biomedical research by private charities, or in the dependence of research on public agencies are pivotal elements in private-public partnerships in biobanking.

Such differences also apply to biobanks. Thus, it has been said that “Commercial biobanks are attempting to position themselves as a, if not the, solution to problems that include a lack of public trust in researchers and lack of financial resources to support the prospective creation of collections that meet the highest scientific and ethical standards in the non-profit sector” [5]. This loss of trust is partially secondary to some examples of unethical practices that occurred in the past, and it has been suggested discomfort with the idea of gain from the mere transfer or exchange of human genetic material and information. However, this is not the actual situation in most of Europe, where academic research and researchers enjoy a high level of public trust, which is clearly higher than for industry-related research.

These differences and nuances cannot be discussed in depth in this chapter, and

only general aspects can be included. Below we will focus on the Spanish social environment, which is characterised by a strong and very highly qualified public health system, little development of private charities funding biomedical research and hence a great dependence of research on public domestic or international (EU) agencies, and an increased presence of international pharmaceutical and biotechnology companies. The authors invite the readers to extend these thoughts to their own specific social environment.

THE PRIVATE AND THE PUBLIC SECTOR: TWO SECTORS WITH SPECIFIC OBJECTIVES, RESOURCES AND SKILLS

As was said above, both sectors (public and non-profit private institutions on the one hand and commercial institutions on the other) are involved and interested in the promotion of health, albeit with different and usually complementary objectives. While for the public sector, health promotion is the main objective, for the industrial sector, given its commercial character, profit is more important, although these are also important considerations in the academic setting. However, this basic difference in objectives is not an impediment to the need for both parties to establish efficient and effective ways of collaboration, especially in countries with advanced health systems of public character.

The private-industrial sector has the best capabilities for drug discovery and commercialization, biotechnology innovation, and the development of new products in order to facilitate biomedical research and public health. However, they usually have more difficulties accessing human samples and their associated clinical annotations, including adequate and long-term follow up, especially in those countries where the public sector is the most important agent of health care. On the other hand, the clinical sector (more frequently public in Europe) has more easy access to patients and healthy donors through hospital-based biobanks and is more dedicated to basic, translational and classic clinical research, but it is aware that it is not competent in the specific areas where industry has more expertise, resources and skills, and in fact almost only industry translates research into products [6].

However, the general landscape has changed in recent decades. Until the 1970s, academic research rarely worked on applied technologies, but the revolution of molecular genetics has enabled investigators to study, isolate and produce a large amount of molecules with medical properties. On this basis academia promotes a new era of relationships with industry, either directly or by using their own institutional offices for filing patents and licensing intellectual property to companies [6, 7].

These relationships certainly represent a great opportunity for solving health

CHAPTER 2

Models of Collaboration and Experiences between Bio-Industry and Academic Biobanks

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Abstract: Access to high quality human biological samples and associated medical information is an essential prerequisite to biomedical research and innovation for both academia and industry. In particular, the private industry sector needs access to biospecimens and data to develop innovative products to keep or gain market leadership. Interaction between industry and academia is important from a social and economic stand point. One provides sustainable global economy while the other contributes to the scientific knowledge base. The main challenge in such collaborations is reconciling perceived altruism and open collaboration with intellectual property and profit. In order to establish a fruitful collaboration, the partners need to recognize their differences to produce positive outcomes for both and avoid the potential drawbacks that different cultures can encur when attempting to join forces. As seen in previous chapter, biobanking is indeed a liaison between the public and private realms. Models for partnerships must be characterized by a common vision, shared mutually agreed goals, clear commitment and investment from all partners through formalized collaboration and shared decision-making.This chapter focuses on the elements necessary for successful collaboration between public and private realms and looks at various models of collaborations, from traditional models,that existed before biobanking was recognized as a discipline, to recent models of public-private partnership. These include models directly created for private collaborations with biobanks as well as models of collaboration where biobanks play an integral part. The chapter concludes with suggestions for innovative models of public-private synergy in biobanking for the future.

Keywords: Charitable-trust, Consortia, Data banks, Expert centers, Honest-broker, Intellectual property, National biobank, Networks, Public trust, Research, Safe-harbor, Service, Umbrella initiative, Validation studies.

INTRODUCTION

In a perfect world, a perfect model of collaboration would be one where the tangible and intangible investment of the various partners is recognized and

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valued. Translating this principle to biomedical research means that biobanks and public health care systems would have full recognition for the true value of the cost of collecting and annotating the samples, including the entire effort of clinicians, pathologists, nurses, technical personnel that process and collate the information. The university system would have acknowledgement for the education and training they provide to create the minds that invest in these systems, and for their investment in technological platforms and basic research that informs the later processes of translational and applied research.Private industry would have the benefit of the biobanks samples and data and reduced R&D costs through collaboration with academia to develop companion diagnostics and therapies [1]. All of this would feed back into a public benefit to the health care system from which all originates by providing lower costs diagnostic tools and pharmaceuticals. However, this is not a perfect world so no model of collaboration is perfect. From this perspective, we present a series of models of public-private partnership (PPP) in biobanking which include basic traditional forms of collaboration that still function on a smaller scale and more innovative models that attempt to approach this idea of a perfect world and suggest some to fuel those already envisioned.

PPP COLLABORATORS

Models of collaboration intrinsically depend on the type of partners involved in the collaboration itself. So before looking at the possible models for collaboration between public and private realms, it is important to consider the collaborators, understand their point of view, and look at the elements of synergy to evaluate what models work best for certain situations.

Academic Biobank Structures

The academic environment is very heterogeneous. It encompasses undergraduate and graduate education and a diverse faculty with disparate goals and measures of success. The basic scientist has to publish, the clinician is promoted based on doing good clinical work and disseminating that knowledge, and the clinician scientist is trying to expand the translation of science to patients and expand patient care beyond the institution. It is usually either the clinician and/or principal investigator (they may be one and the same) who has contacts with industry. Through collaborations with industry, academia may possibly access increased funding, potentially increase its output through publications and, in some cases, become part of international networks. They are also afforded the opportunity to do research on the advanced end of the research process in the biomedical field to help produce something that is more effective than a costly patent. The relationship that the biobank has with its hospital and academic

contributors will affect its involvement in any collaboration. Biobanks that are an integral part of a larger infrastructure such as a research center will have more extensive platforms at its disposal. They will also have the capacity to develop internal research projects and their collaborations will be facilitated by these add on services.

Industry Partner

The bio-industry that requires access to biobanks and biospecimens divides itself into two groups, companion diagnostics and the pharmaceutical industry. It has been easier for the former to collaborate with academia and academic or public hospital biobanks on validation studies for the diagnostic test as the amount and treatment of information required to validate diagnostic tests does not, in general, infringe on the privacy of the patient or healthy individual acting as a control. Pharmaceutical companies,have historically performed the majority of their drug discovery research in house and only collaborated at the stage of clinical trials, The era of industry sustaining completely in-house R&D activities has gone [2, 3]. Industry have realized that they need to change their research models to remain viable. Industry must find ways to outsource these activities and academia has the resources to potentially respond. This has created the possibility for new models of collaboration with academia in order to perform research and with biobanks as the underlying research infrastructure and the provider of samples and data.

Small and Medium Enterprises

(SMEs) have the most to gain by collaborating with academia. As they have limited research resources, collaborating with academia affords them greater research capabilities and platforms with which to execute important validation studies. SMEs have less administrative structure, which can be a double edge sword. While it means they can be more flexible, it also means that less structure within the private organization combined with the un-structured academic research approach can be detrimental to achieving a result. It does however create a more open environment when discussing issues of intellectual property. SMEs fit more comfortably into the mission of academia as they are seen as one step beyond a university spin-off. Collaboration with SMEs, if carried out within the university are then considered part of the invaluable education and progression the university must provide for its researchers [4].

Government & Public

The general public is the partner that should gain the most from any partnership. The end result of any efficient research cycle is the provision of more cost-efficient and targeted treatment and thus an improvement in health care services.

CHAPTER 3

Quality Management System for Research Biobanks: a Tool to Incentivize Public-Private Partnerships

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Abstract: Biospecimens are essential raw materials for the advancement of applied biotechnology. Awareness of the importance of sharing biospecimens has increased in recent years and biobanking activities have facilitated access to them. However, the sharing of such samples for Research & Development could be considerably improved if there were a recognised global agreement about the standard by which to compare their quality.

The Organization for Standardization (ISO) is the internationally recognised body that provides guidelines and defines specifications to ensure standardisation of materials, processes and products.The working group two (WG2) of the ISO Technical Committee (TC) 276 established by the ISO on Biotechnology is dedicated to Biobanking. The aim of this working group is to establish sets of standards that apply to the biobanking field, to include human, animal, plant and microorganism samples, thus ensuring that they are of appropriate quality. The availability of worldwide recognized policies and procedures will support access and exchange of samples and related data, giving a major impetus to global use of bioresources for market application.

The standard set, which will be based on existing documents and guidelines, will be the foundation of a quality management system (QMS) specifically for biobanking. ISO QMS would enable the establishment of ad hoc global certification that products, processes and/or services conform to relevant standards, technical specifications and guidelines.

Keywords: Accreditation, Biobanking, Bioeconomy, Biological resources centres (brc), Bioresource, Biospecimen, Biotechnology, Certification, Guidelines, Harmonization, International Standard (is), International standard organization (iso), Market, Personalized medicine, Quality Control (qc), Quality Management

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System (QMS), Repository, Standardization, Technical committee 2761.

1. QUALITY REQUIREMENTS: A BRIDGE BETWEEN PUBLIC AND PRIVATE SECTORS

Public and private sectors are often based on different principles and language. Two of the critical issues in the establishment of Public Private partnership (PPP) in biobanking are represented by a common ground for defining biospecimens and for comparison of available biological resources. Standardization of requirements for the quality of biospecimens would provide a useful tools to overcome some of the major difficulties in facilitating fruitful exchange of samples and data for the development of both research and market applications.

1.1. From the Roots of Quality to Management System Standard(s) [MSS]

Q*uality* is an historic concept which has its roots in the late 13th century, when craftsmen began organizing into guilds responsible with strict rules regulating the quality of products and services This approach was followed until the early 19th century. During the 20th century, the idea of Total Quality Management began to emerge as we know today, and for the first time statistical theory was applied to product quality control (QC). The early work of Shewhart in drafting statistical methods for process control was later developed by Deming in the Plan-Do-Check-Act (PDCA) theory [1]. The four phases in the PDCA Cycle involve:

- Identifying and analyzing the problem (Plan)
- Developing and testing a potential solution (Do)
- Measuring how effective the test solution was, and analyzing whether it could be improved in any way (Check)
- Implementing the improved solution fully (Act)

Plan–do–check–act is an iterative four-step management method used in business for the control and continuous improvement of processes and products. The early work of Shewhart and Deming [2] constitutes much of what today comprises the theory of statistical process control. However, there was little use of these techniques in manufacturing companies until the late 1940's.

During its history, quality management (QM) has gone through numerous changes, but the aim remains the same: to improve customer satisfaction. Therefore, the quality of a product may be defined as "its ability to fulfil the customer's needs and expectations". However, quality needs to be defined by criteria which vary from product to product. For "concrete items", the term quality applies and refers to the degree to which a set of inherent characteristics fulfil a set of requirements. For mechanical or electronic products, quality

requirements include performance, reliability, safety and appearance, while quality standards for pharmaceutical products need to involve physical and chemical characteristics, medicinal effect, toxicity, taste and shelf life [3]. Often it is a chain of processes (procedures to transform inputs into outputs) that deliver a product or the final object. Thus, a "process approach" is a management strategy that allows the management and control of the processes that make up the organization. A management system may be restricted to a specific function or section of an organization, it may include the entire organization or it may even cut across several organizations. There are many types of management system including, for example, environmental management systems, disaster management systems, risk management systems *etc*. Many of these include a quality management system (QMS).

Thus, a QMS is a set of interrelated or interacting components that organizations/ industries/bodies use to formulate quality policies and quality objectives and to establish the processes that are needed to ensure that policies are followed and objectives are achieved. The QMS involve human and material resources, structures, organization, plans, processes and tracking. In other words, a QMS is nothing more than good business sense and is the establishment of policies, processes and controls that can impact on the organization's ability to meet customer requirements and there is a big effort to apply it also in biobanking [4].

The quality policy and objectives of QMS are achieved through quality assurance (QA) and QC, which, respectively, focus on the processes through which the product is produced and on the product itself.

A QMS is linked to the important concept of the external recognition of quality, which relates to requirements specified in Licenses to Trade, guidelines, specified customer requirements, and the chosen management system standard(s) [MSS].

1.2. Biobanking Worldwide: State of Art

Biological materials, including samples from humans, animals, plants and microorganisms and/or their derivatives are a major resource for the advancement of food industries, human and animal health and Research & Development (R&D) in life sciences. Activities related to sampling, cataloguing, studying, storing and distributing biospecimens are known as biobanking. In the last decade biobanking has spread widely in terms of both of new sites and developing solutions for the exploitation of sector potentialities. This increased global interest has produced many studies concerning biobanking activities, management and networking, and also related issues including legal, ethical, quantity *vs* quality aspects of biological resources and their sustainability [5].

CHAPTER 4

Quality Criteria in Oncology: Lessons learned from the B4MED Biobank

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Abstract: Since the beginning, the scientific research was an integral part of the mission of the European Oncology Institute (IEO). Its position is at the intersection between Surgical Units, the Department of Pathology and Research Units. This organization makes the IEO Biobank for Translational Medicine (B4MED) a critical resource that reflects the mission of IEO to perform "Research for Care".

The B4MED collects, catalogues and stores biological samples that are non-essential for diagnostic purposes from patients who provide informed consent for the use of their tissues for research purposes. A direct pipeline with the operating theatres for the collection of tissue samples ensures negligible sample degradation. Surgically-excised pathological and non-pathological tissue samples, plasma/serum, total blood, DNA and RNA are collected and stored according to specific protocols and standard operating procedures. All biobanked samples are managed and tracked through a software package that is fully integrated with the hospital medical records database, pathology database and central registry of patient demographic information. This ensures that each sample is linked to a full complement of anonymous or anonymized (according to patient choice) patient information that is accessible solely by authorized Biobank personnel.

The high quality biospecimens collected by the B4MED are used for biomarker and drug discovery experiments, both for basic research and for clinical research, with the ultimate aim of providing excellence in patient care through excellence in research.

Keywords: B4MED IEOBiobank for Translational Medicine Unit, Handling, Participation Pact, Pathological and non pathological, Sample collection, Storage and news approach for the pathologist work, Trust-based consent.

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INTRODUCTION

In the last two decades, progress in biomedical disciplines has made fundamental steps towards the identification of pathogenic processes, genetic disorders, specific pathways and molecular targets in inflammatory and oncologic diseases, that has open up the new era of targeted personalized medicine [1, 2].

These achievements have been possible also thanks to the implementation of biobanks which are collections of different human biological samples organized following strict ethical, statistical and biological procedures [3, 4].

In this chapter we will discuss important requirements of a modern biobank by describing the organization and quality control criteria implemented from the tissue bank of the European Oncology Institute (IEO) based in Milan, Italy (*i.e.* Biobank for Translational Medicine Unit).

This biobank collects catalogues and stores biological samples (namely, surgically excised tissue samples non-essential for diagnosis, plasma/serum, total blood, DNA and RNA) donated from patients who provided informed consent for the storage and use of their tissues and cells for research purposes. In particular we will report the comprehensive pipeline that links in traceable and semi-automatic way the various phases of the process that include: a) the collection of a new form of trust-based consent (the so-called Participation Pact), b) the collection and processing of tissue samples, cells, plasma, serum, total blood, DNA and RNA that are subsequently stored according to specific protocols and standard operating procedures (SOPs).

Additionally, primary cell cultures, stem cell preparations, and tissues from animals xenotransplanted with tumors are stored in our facility, by providing researchers and physicians with valuable biomaterial for research purposes.

The Participation Pact A New Form Of Trust-Based Consent

The first issue to be considered in relation to the collection and storage of human biological specimens is about the ethical requirements to be met for legitimate use of samples and it refers to the informed consent of subjects participating in research using their biological materials and or associated data.

With regard to this issue, only biological specimens deriving from patients who have signed a specially designed informed consent for research purposes are accepted to be banked in our facility [5, 6].

Accordingly a new form of trust-based consent for research biobanks has been specifically implemented [7]. The trust-based consent, the so-called Participation

Pact(P-P), has two fundamental features.

Firstly, it defines a new form of relationship between researchers and participants based on mutual trust. In this way, the two parties are bound by a pact, which prevents the relationship from being unbalanced and forces both parties to respect the agreement they have forged [7].

Secondly, participation in research is completely transformed. Unlike previous models that attempted to impose on participants a robust duty to participate in research [7], a pact-based relationship instead provides participants with a strong incentive to do so, as they are motivated by an act of solidarity where reciprocity, trust and the belief that science is an ethical enterprise play mutual supportive roles [7].

With the P-P, patients can choose whether or not to donate samples for research purposes and are offered the choice of samples being held either anonymously or being anonymized with a specific encryption that avoids to retrieve patient identity compliant with privacy National laws [7].

Furthermore, audio-visual material has been prepared to explain the main features of the P-P and to help patients make fully informed decisions to participate or not to our research programs by donating biological samples. To ensure maximum compliance, trained Biobank research nurses are always on hand to explain to patients the impact and implications of their decision [7].

Collection and Management of Data Relating to Samples

All biobanked samples are managed and tracked through a software package that is fully integrated with the hospital medical records database and pathology database. This is essential in order to timely manage high quality clinical data linked to all biospecimens collected by the Biobank for Translational Medicine Unit.

These specimens are then used for biomarker and drug discovery experiments, both for basic research and for translational research projects (*e.g.* the development of personalized therapies), with the ultimate aim of providing excellence in patient care through excellence in research.

This was also achieved by the integration of its activity with the Department of Pathology, which ensures the continued and centralized supervision of a dedicated pathologist in the processing of biomaterials in an *ad hoc* structured core facility. Specimen collection can be institutional or linked to a specific project driven by a researcher.

CHAPTER 5

Rights and Obligations of Different Stakeholders Involved in Access and Use of Samples and Data in Biomedical Research[1]

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Abstract: Millions of human biological samples and associated data are collected each year for a variety of purposes. These purposes may include basic research, clinical trials and epidemiological studies. The legal framework that determines access to biobanks remains presently unclear. The absence of a defined set of applicable rules on international, European and national level creates legal uncertainty for biobanks and applicants. This chapter reports on four studies concerning the legal structure applicable to "Access to Biobanks". The first study consisted of a comparative analysis of access arrangements of organizations, biobank networks and biorepositories. The second study included interviews to gather qualitative data on the different perspectives held by stakeholders and experts in relation to the rights and obligations of custodians and applicants with respect to access to HBM and data stored in biobanks. The third study focused on the analysis of the legal framework applicable to access to biobanks. The final study (four) analysed the intellectual property rights (IPRs) in biobanking and the return and sharing of research results. These studies allowed us to formulate recommendations on the improvement of the legal framework applicable to public and private biobanks.

Keywords: Access, Biobank, Custodianship, Intellectual property, Legal framework.

INTRODUCTION

The European Strategy Forum on Research Infrastructures (ESFRI) identified biobanks as one of the main priority research infrastructures for the European Research Area (ERA) for the next 10 to 20 years [1, 2]. The 'Biobanking and

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Biomolecular resources Research Infrastructure' (BBMRI) was one of the first projects established under the European Research Infrastructure Preparatory Phase of ESFRI [3, 4]. The European Commission recognized the sound governance of biobanks as one of the most important challenges for the European innovation system [5].

For more than 100 years, millions of samples of human biological material (HBM) and associated data were collected in biobanks for a variety of purposes. These purposes included, for instance, basic research studies, clinical trials and epidemiological studies [6 - 8].

The exact definition of 'biobank' differs across countries. In Belgium for instance, article 2, 27° of the Belgian Act on HBM of 19 December 2008 defines a biobank as: "a structure that obtains, processes, stores and provides human bodily material and possible also associated data and *this (only) for scientific research purposes,* excluding research that implies medical applications to humans." (underlining by the authors). The rise of new scientific disciplines, such as genomics, proteomics and bioinformatics and new sequencing technologies in association with the initiative of precision medicine (PM) [9] considerably increased the demand for the systematic collection of large amounts of high quality human biological material (HBM) and data [3, 4]. The use and access to HBM and data stored in public biobanks has therefore become a crucial component in many biomedical research projects [10, 12].

Collections of HBM and data vary in scope, form and scale, according to the type of HBM and data that are retrieved and the different purposes for which they are used [13]. The scale ranges from small collections in hospital or university departments to the storage of large amounts of HBM in specifically designed and well-equipped facilities publicly or privately funded [8, 14].

Access to large amounts of HBM and data is crucial for many biomedical research projects. That is why several initiatives have been taken to develop biobank networks to share and combine different collections of HBM and data. The concept of a 'biobank network' can be defined as '*a group of institutions who freely assume the commitment to collaborate in the domain of biobanking and who (often) share the same procedures and quality policies, and who are (or might be) helped by a central hub for coordination in terms of service' [15].*

Different aspects determine the value of a biobank or biobank network. The quality of the samples and associated data and the ability to link the samples with donor information are two of these factors [16].

In the realm of translational research, biobanks and biobank networks will take a

central place in the R&D process of medicines. Biobanks can provide a crucial platform for international and interdisciplinary cooperation and act "as key drivers for next generation biomarker (diagnostics) research and drug discovery" [17]. Good functioning models for access to HBM and data are crucial.

The legal framework that determines access to biobanks or biobank networks often remains unclear. The absence of a defined set of applicable rules creates legal uncertainty for biobanks and applicants. Our study investigated the hopes and concerns of the different stakeholders focusing on custodians of public biobanks and public and private applicants in biobanking. It mapped and characterized the present heterogeneous legal framework applicable to biobanks and formulated recommendations for the development of transparent, feasible and encouraging legal rules suitable for access to biobanks and biobank networks.The authors define custodianship as the "caretaking responsibility for HBM and data that starts at the planning of a biobank initiative, prior to the collection, and continues through research use to final dissemination of research results" (a slight adapted version of the definition used by R. Yassin *et al*. and the National Cancer Institute [34]).

Access Conditions to Biobanks and Biobank Networks

Theoretical and empirical research methods were designed and used to perform the studies [18 - 20] reported in this chapter, including literature reviews, interviews and in-depth document analyses.

A comparative document analysis of access arrangements of organizations, biobank networks and public as well private biobanks [19] is described here. This analysis provides qualitative data on the extent to which access arrangements contain information on selected access conditions. It furthermore considered to which extent access arrangements implement those access conditions in a harmonized way.

Furthemore, a comparative study of the legal framework that is applicable to access to biobanks [18] is described. This comparative study started with a general overview of the national legislation applicable to biobanks in Belgium and Denmark and legal norms at the international level and at the level of the Council of Europe. It also analyzed the rights and obligations of custodians of biobanks, applicants and - to a lesser extent– donors in these different legal instruments.

The last study reported in this chapter [20] entails a legal analysis of intellectual property rights (IPRs) in biobanking and to a lesser extent the return and sharing of research results. This study provides an overview of the most relevant IPRs in biobanking and discusses the risks and opportunities associated with the identified

CHAPTER 6

HUB Organization to Enhance Access to Biological Resources: a French Example

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Abstract: The main purpose of biobanks is to provide private and public organisations with biological resources to be used for research projects but unfortunately this process is often not straightforward. Most biobanks supply biological resources to research teams within their own organizations and have difficulty in supplying samples to external teams. The most difficult step is to obtain a specific collaboration agreement between the two parties. This step takes a long time and often interferes with research planning. Moreover, most of French biobanks are administered and financed by hospitals or public research institutes, which established the biobanks for the purpose of supporting their own researchers. The supply of biological resources in the absence of scientific collaboration was not a part of the original plan. Yet today these biobanks need to supply research teams in private/commercial organisations, to promote the use of their samples, to develop translational research and to obtain a return on investment. The rights and needs of researchers must be take into account but priority must be given to the valorization of the biobank. To encourage optimal use of samples and avoid the costly conservation of unused collections, we propose a "HUB" organization to enhance access to biological resources in France. The development of this organization and drafting of legal agreements must take into account the following considerations: a) the researchers' current needs must be fully understood: this depends on excellent communications between the HUB and legal representatives of the research teams, and b) the availability of collections through a biobank network must be fully understood: this depends on excellent communications between the HUB and legal representatives of the biobanks.

Keywords: Biobanks, Biobank sustainability, Biological resource centres, Collection, Contract, MTA, Public-private collaboration, Supply.

INTRODUCTION

Research in academia and industry often requires large sets of biological samples to develop new programs or to validate a scientific concept. The process of

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obtaining sufficient samples that meet quality criteria defined by international standards is often time-consuming for researchers and reduces their competitiveness. In response to their needs biobanks have been developed over the past 20 years to manage sample collections under standard operating procedures and to ensure that the quality and ethical requirements of international recommendations [1, 2] and national regulations are met. So, gradually, biobanks have become an important provider of biological resources for researchers [3, 4].

However, in general biobanks have focused more on ensuring sample quality by efficient collection and storage of materials, and less on the efficient distribution of samples to researchers. This is a consequence of the fact that most biobanks distribute samples to researchers who initially collected samples (clinicians) or at least to researchers who are linked to the biobank in some way (*i.e*, through a scientific relationship) as demonstrated by findings of the European report [5]. Even in the case of an open sharing policy, they usually give samples to academic teams without charging a fee for the service. Similarly, a study of US biobanks demonstrated that only 2% of them charge a fee for samples [6] and a Canadian study found that cost recovery ranged between 5%-25% of the actual cost [7]. This situation is due to the fact that most biobanks are financed by public funding or per-project funding [8].

Despite these models, the economic situation is more stringent globally and the cost of biobanking activities continues to grow. Academic biobanks need to be as competitive as commercial biobanks which usually develop business to meet the demands of pharmaceutical companies [9].

Even if some reports estimate that biorepositories can save millions in research funding [10], it is clear that biobanks today will need to find adequate and reliable sources of funding to be sustainable in the long-term [1, 11]. It is possible to have an optimistic view of biobanking development. Many repositories have very under-used collections, so by improving access to these collections we may be able to meet some of the growing demand for human biospecimens.

A return-on–investment policy is necessary to maintain the high quality of collections and ensure biobanks sustainability through a model which takes into account the relationship of altruism and solidarity between donors and biobanks [12]. There are more and more publications that present such models as business plans [13 - 16] and demonstrate that creating viable funding models is a pre-requisite for the sustainability of biobanks.

These developments encourage academic biobanks to face difficulties they must overcome to become sustainable. To this end, biobanks are involved in the development of tools such as catalogues [17], harmonised operating procedures

[18], and processes for request management to strengthen communication and promote demand. In the same way tables of costs have been established and published [19, 20] in order to provide biobanks with standard prices for services. Even though it is unethical to sell human samples, all the processes around collection, storage and supply of human samples can be costed. For example, the Canadian Tissue Repository network developed a tool to calculate the appropriate user fees [21]. In France, the billing policy for biobank services has been published in "Journal Officiel de la République Française" in a specific chapter on clinical activities.

Networks of biobanks can also contribute to sustainability as for example where a number of biobanks work together to add value to a collection [22]. Another type of biobank network, based on a Hub model might be particularly useful for enhancing sample exchange: according to this model a third party would act as a Hub, linking sample suppliers and sample requesters in a win-win collaboration.

The HUB MODEL

Initially developed by airline companies to improve traffic at the airport, the Hub concept is based on a central interface facilitating trade. In the case of research, some Hub organizations have been described which facilitate harmonization of sample management [23] and synergy between different partners [24]. The Hub solution has been explored in order to deal with the requests for samples and the wish to supply samples with the aim of quick movement of inputs (the requests for samples) and outputs (the supply of samples).

HUB-BTB-3CR is a Hub organisation developed by BioTech BANK and 3C-R. In this organisation, sample requests are managed centrally by a central node (the HUB) so that researchers working in the public or private domains can have direct access to all biobanks that belong to the HUB-BTB-3CR (Fig. **1**).

HUB provides linkage between the researchers' needs (most of them are from pharmaceutical or biotechnology companies)and a network of biobanks which can provide them the samples. Through the HUB all the sample requests are shared with all the biobanks in order to provide the opportunity to match the needs of the two parties quickly. This model is particularly effective and useful in the case of requests for rare disease samples.

For the HUB-BTB-3C-Rorganisationto be successful, there are the following requirements:

- there must be a large number of biobanks able to respond quickly to requests,
- the researcher's needs must be well defined and well understood,

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Elena Salvaterra

Elena Salvaterra is a jurist doctor (JD) and Ph.D in Law of Science (Medical Law and Ethics). After a few years spent at academia (University of Milano, Italy), she collaborated with the Biological Resource Center of the Polyclinic University Hospital in Milan as a social scientist. She co-founded with Dr. Paolo Rebulla, a hematologist, the Laboratory of Bio-Law dedicated to the study of ethical, regulatory, economic and social aspects associated with therapeutic (namely stem cell) and research biobanks.

Since 2009 to 2014, she worked in the research institute "E. Medea" where she coordinated several projects on pediatric biobanks. From 2014, Dr. Salvaterra collaborated with private national and international companies as commercial and regulatory consultant.

She is presently engaged as a consultant at Exem Italia where she is the coordinator of scientific projects and regulatory affairs related to biobanks. She is also a member of the Scientific Advisory Board of CloudLims working in healthcare IT.

She is a member of international scientific organizations related to biobanking and organ banking such as ISBER, ESBB, the Society for Cryobiology and Organ Preservation Alliance based in California at the NASA Science Park.

Besides being the author of several publications and invited speaker at numerous academic (including Harvard Medical School) and commercial conferences, she is also the author of books about biobanking. She published "Regulating biobanks in humans; The use of adult and children biomaterials for clinical and research purposes" in 2014 and the ebook "Advances in biobanking practice thorugh public and private collaborations" (under publication with Bentham Science Publisher). Elena Salvaterra received several recognitions for her work in biobanking from the scientific committees of several international conferences. She is a humanist of science with comprehensive knowledge and experience of healthcare policy and management.

Julie Corfield

Julie's (Founder of Areteva) expertise includes biobanking strategy and capabilities, exploratory research collaborations and early clinical development projects (concept to delivery) project management (R&D/ public-private consortia). Her specialist interests are, biobanking policy, Biobanking law and bioethics, R&D governance, tissue acquisition strategy and acquisition for all phases of the R&D cycle, Best Practice in sample logistics, Biobanking infrastructure, RFI/RFP processes, and business change projects. Julie, over the last 20 years, has established herself as a biobanking specialist and a project manager, within AstraZeneca and externally. This includes roles as a biobanking specialist and a project manager for public-private partnerships and she is also leading a consortium in the grant application for a UK Biobanking project. In AstraZeneca, as a designated individual, she was legally accountable for the biobank at the R&D site and led global R&D change projects covering all aspects of Biobanking. For respiratory and inflammation disease areas, her focus was on defining and implementing tissue acquisition strategies/exploratory research collaborations. As a clinical operational lead, she has extensive experience in clinical development and the implementation of early development programmes for various disease targets.