Bio-repository of Post-clinical Test Samples at the National Cancer Center Hospital (NCCH) in Tokyo

Koh Furuta1, Karin Yokozawa1, Takako Takada1 and Hoichi Kato1,2

1National Cancer Center Hospital and 2National Cancer Center Center for Cancer Control and Information Services, Tokyo, Japan

Received March 9, 2009; accepted April 20, 2009; published online June 1, 2009

We established the Bio-repository at the National Cancer Center Hospital in October 2002. The main purpose of this article is to show the importance and usefulness of a bio-repository of post-clinical test samples not only for translational cancer research but also for routine clinical oncology by introducing the experience of setting up such a facility. Our basic concept of a post-clinical test sample is not as left-over waste, but rather as frozen evidence of a patient’s pathological condition at a particular point. We can decode, if not all, most of the laboratory data from a post-clinical test sample. As a result, the bio-repository is able to provide not only the samples, but potentially all related laboratory data upon request. The areas of sample coverage are the following: sera after routine blood tests; sera after cross-match tests for transfusion; serum or plasma submitted at a patient’s clinically important time period by the physician; and samples collected by the individual investigator. The formats of stored samples are plasma or serum, dried blood spot (DBS) and buffy coat. So far, 150,218 plasmas or sera, 35,253 DBS and 536 buffy coats have been registered for our bio-repository system. We arranged to provide samples to various concerned parties under strict legal and ethical agreements. Although the number of the utilized samples was initially limited, the inquiries for sample utilization are now increasing steadily from both research and clinical sources. Further efforts to increase the benefits of the repository are intended.

Key words: bio-repository – post-clinical test sample – limited storage system – clinical laboratory – bio-bank

INTRODUCTION

We established the Bio-repository at the National Cancer Center Hospital (NCCH) in October 2002 and arranged to provide samples to various concerned parties under strict legal and ethical agreements (1).

The NCCH is located in the central area of downtown Tokyo. The aim of this hospital is to provide successful treatment of cancer patients and follow-up observation of patients whose cancer is in remission or cured. This hospital has 600 beds, the annual outpatient number is ~250,000, and the annual hospitalized patient number is ~200,000. The annual laboratory test number is 2,500,000 for outpatients and 1,700,000 for hospitalized patients. These figures indicate that a huge number of blood samples are phlebotomized daily in this hospital. Initially, we began storing samples just in case a repeated test was required for the various clinical necessities. In the course of time, these samples accumulated and we established a large repository. Further, we found out that most of the stored samples were being discarded without repeated tests. Based on these conditions, we decided to provide part of the samples to the research communities. Besides these, the recent increase in demands from industrial, academic and government entities for bio-samples has extended the trend worldwide toward establishing various bio-repositories (2–4).

Although there exist many bio-repositories of post-clinical test samples, no articles reported the importance and usefulness of a bio-repository of post-clinical test samples. One of
the reasons for this could be that post-clinical test samples are regarded as simply ‘left-over’ and never receive attention as a serious research resource. In this article, we would like to change this concept and show that post-clinical test samples are not left-over waste (5) but an important resource by introducing our experience of setting up a bio-repository of post-clinical test samples.

PATIENTS AND METHODS

SAMPLES

POST-CLINICAL TEST SAMPLES

All the samples we presently handle are derived from patients who are either outpatients or are in the hospital setting.

AREAS FOR SAMPLE STORAGE

The areas of sample coverage are the following (Fig. 1):

i) Sera after routine blood tests.
ii) Sera after cross-match tests for transfusion.
iii) Serum or plasma submitted at a patient’s clinically important time period by the physician.
iv) Samples collected by the individual investigator. The Repository is expected to act as a surrogate sample collector.

FORMATS

To respond to various needs, we attempt to store samples in as many formats as possible, such as plasma or serum, dried blood spot (DBS) anduffy coat (Fig. 2). Most of the volume of initial samples of whole blood format is 4–7 ml in quantity. Naturally, the volume of the plasma or serum could be 2–3 ml. We aliquot these 2–3 ml into each 1 ml cryo-tube. We understand that the less volume per each cryo-tube is better for future thawing. This ‘small volume strategy’ has a drawback. We need a lot of cryo-tubes and also extra space. The current 1 ml size is based on a balance between funding and quality assurance of samples.

STORAGE

STORAGE SYSTEM

We adopted a system of ‘Limited’ storage. Most of the samples after 5-year storage are to be released from the Repository. As an exception, very valuable samples can be stored for >5 years. Thus, in a sense, we have adopted a modified limited system. A decision for >5-year storage is based upon a request by a researcher and/or physician. Before releasing samples from the repository, we distribute a notice and ask researchers and/or physicians to identify any of their valuable samples for >5-year storage value.

SOFTWARE

As a managing database, FreezerWorks (Dataworks Development, Mountlake, WA, USA) has been utilized.

STORAGE SPACE

Among the samples stored, plasma or sera are stored in a −20°C cold room of 90 m³. The DBSs are stored at room temperature. As a DBS format, 10 µl of blood per each well (GenPlate DNA Storage Kit, GENVAULT, Carlsbad, CA, USA).

Figure 1. Samples for storage. The areas of sample coverage are as follows. (A) Sera after routine blood tests. (B) Sera after cross-match tests for transfusion. (C) Serum or plasma submitted at a patient’s clinically important time period by the physician. (D) Samples collected by the individual investigator.
USA) is stored. The buffy coats are stored in a \(-80^\circ\text{C}\) deep freezer of 728 l.

**SAMPLE UTILIZATION**

**PROCEDURES FOR SAMPLE UTILIZATION**

Each patient entering our hospital must provide permission or denial for utilization of one’s samples for other than one’s personal clinical necessity (Fig. 3). We call this an all-inclusive informed consent (IC). If a researcher wants to investigate the samples derived from a patient, the particular protocol must be approved by the Institutional Review Board (IRB). After this initial procedure, the researcher has to search for and select the patients samples needed from the patient clinical database. Among the records of the selected patients, the researcher has to search for and select the samples required. Then the researcher has to check for the existence of the samples in the Repository. As a final procedure, the researcher has to check the status of the all-inclusive IC. The researcher can utilize the samples with an affirmative status of the IC. It is to be noted that three information systems such as the clinical information system, the clinical laboratory data processing system and the bio-repository system are physically independent. In other words, there are no direct connections among them electronically. Each sample is assigned a unique ID, and this particular ID is different from the patient’s ID number. These IDs are linked but are strictly controlled by authorized personnel only.

**RESULTS**

As mentioned earlier, the bio-repository opened in October 2002. The DBS format began in May 2006. Further, the buffy coat storage began in January 2007.

**FORMATS**

So far, 150 218 plasmas or sera, 35 253 DBS and 536 buffy coats have been registered for our bio-repository system (Table 1). Although we tried to widen the formats for storage, the main frame of the storage is still regular sera or plasma. The coverage of stored 150 218 plasmas or sera are as follows (Table 2).

**SAMPLE UTILIZATION**

The bio-repository has provided its stored samples to various investigators, either in clinical research or in translational research (6–10) (Table 3). Example 1 (6) indicates the clinical studies and Example 2 (7) indicates the translational, such as proteomic study. In either type of study, clinical
information attached with samples was very important. Further, we initially were concerned about the quality of the samples for translational, especially proteomic study; however, most of the samples we provided were accepted.

**Cost of Repository**

The cost of maintaining a bio-repository such as ours is substantial. Fortunately, the Bio-repository is in the Clinical Laboratory division of the hospital. Thus, we can utilize and share the facilities and cut the total cost for the repository. The total cost of regular supplies is $30,000/year. Further, the personnel cost is $20,000/year. The *ad hoc* costs were mainly covered by donations from various in-hospital doctors.

**All-Inclusive Informed Consent**

All-inclusive IC during these 6 years has indicated that there were 0–6.5% denial cases once a patient’s consent existed, and the initial denial rate was 0.8–2.5% (11).

**Discussion**

At first, we wish to indicate several good points of a bio-repository of post-clinical test samples. First, by using post-clinical test samples, we need not ask patients for another phlebotomy for storage purposes. Second, as we showed in the previous sections, even post-clinical test samples can provide various formats of storage, such as sera or plasma, buffy coat and DBS. Third, post-clinical test samples storage can share a variety of laboratory equipment such as centrifuge, freezer and so on, with the clinical laboratories. Also, the repository and the laboratories can use the same supply materials such as cryo-tubes. This means that a repository of this type is economical. Fourth, the strong link between the clinical information system and
samples made it possible to reconfirm the real-time status of the IC, concerning the utilization of the particular samples. To accomplish this, we frequently check the IC status (11,12). Lastly, and this is the most important point among these five beneficial points, a researcher who wants to utilize samples can also utilize clinical information of the particular samples. Our basic concept of a post-clinical test sample is not as left-over waste, but rather as frozen evidence of a patient’s pathological condition at a particular point. We can decode, if not all, most of the laboratory data from a post-clinical blood test sample. As a result, the bio-repository is able to provide not only the samples, but potentially all related laboratory data upon request.

Also, we wish to indicate several key points of a bio-repository of post-clinical test samples. Therefore and most important point is the quality of the clinical samples (13–17). Because our hospital gives much attention to the pre-analytical aspects of sample collection (18), post-clinical test samples in our repository are of at least clinical test quality. Although we do not know how good the quantitative qualities are, the following fact that our samples were accepted and utilized as materials for one project of proteomic analyses in our hospital (7) clearly indicated that the quality of our samples is acceptable. Second, when trying to handle post-clinical test samples, one of the main concerns is an unlimited increase of samples against a limited storage space. To solve this problem, we adopted a system of “Limited” storage. The limited system is based on a dynamic balance between in and out samples. Under the limited storage system, the stored samples are to be replaced or updated regularly. Most of the samples after 5-year storage are to be released from the Repository. Another big concern could be legal and/or ethical ones. We carefully and seriously handle these issues. Three information systems such as the clinical information system, clinical laboratory data processing system and bio-repository system are linked but physically disconnected. Only authorized personnel have access to each system and further strictly limited personnel are privileged to access all systems. Each research project is required to have the IRB approval. We give strict attention toward protection of ethical and legal aspects, concerning human materials as possible.

**Types of Research Best Suited for the Post-clinical Test Samples**

We strongly emphasize, not avoiding redundancy, that unique point of our repository is that we store longitudinally linked samples with ample clinical information of a patient. Clinical information or annotation (12,19,20) literally means the records of diagnosis, past history and therapeutic history. The longitudinally linked samples make it possible for comparison between two points; current and past. In other words, we can do subtraction by using paired samples derived from the same patient. We can subtract the steady or basal state from the increased state of factors unknown. The utilization of the samples from the same patient will contribute a noise reduction of signals other than factors unknown. Further, although retrospective, the ample clinical information provides the opportunities for the researchers to design the best-fit cohort of the studies. The features of subtraction and clinical information, although retrospective in nature, are able to provide good opportunities for bio-marker detection and/or validation (7).

**Potential Uses of the Post-clinical Test Samples**

The strategy of subtraction is quite effective not only in clinical research but also in routine patient care such as diagnostic, adverse effect, nutrition and therapy design fields. Adding the past information to the current patient care will enhance the quality of the routine patient care, especially in the clinical oncology field. Although the number of the utilized samples was still quite limited (Table 3), the inquiries for sample utilization are increasing steadily. Recently, the concept of ‘electronic specimen’ was introduced (21). This particular news article indicated that in the longer term,
samples will be converted into data. Our post-clinical test samples are best fit to this concept. At least, the samples are clinical test quality. Further, longitudinally linked samples are stored and ready to be analyzed. The stored samples can be converted anytime into data in our bio-repository.

Before concluding this article, we would like to emphasize that the potential of post-clinical test samples is tremendous, even under strict legal and ethical regulation. The next challenges for us will be two. Although there are good guidelines issued by the NCI (22) and/or by the ISBER (23), there are no particular guidelines for post-clinical test samples. The first target is to establish standard procedures for post-clinical test samples. This is the quality control of the repository samples. The second target is to establish networks among bio-repositories either domestic and/or international. Then we would like to share this usefulness of post-clinical test samples with the various personnel in industrial, academic and government entities. Eventually, we would like to contribute to the patients of samples.

Acknowledgements

The authors gratefully acknowledge Drs Tadao Kakizoe, Kazuhiro Nomura, Ryosuke Tsuchiya and Setsuo Hirohashi. The authors thank Ms Keiko Hashimoto for her technical assistance. The authors also thank Mr Robert Debold for editorial assistance and manuscript preparation, and Dr Akiko Furuta for her preparing illustrations.

Funding

This work was supported in part by the Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare.

Conflict of interest statement

None declared.

References