Yamada K Y	Isolation and characterization of toxigenic Corynebacterium ulcerans from two closed colonies of cynomolgus macaques (Macaca fascicularis) in Japan	Comparative Medicine	In press		2013
山田靖子	実験動物感染症の現状―結核―	実験動物ニュース	61	64-66	2012
Kanai Y	Frequent GNAS mutations in low-grade appendiceal mucinous neoplasms.	Br J Cancer			2013
Kanai Y	Frequent GNAS and KRAS mutations in pyloric gland adenoma of the stomach and duodenum.	J Pathol			2013
Kanai Y	Prevalence of MED12 mutations in uterine and extrauterine smooth muscle tumors.	Histopathology			2013
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Kanai Y	Pancreatic intraglandular metastasis predicts poorer outcome in postoperative patients with pancreatic ductal carcinoma.	Am J Surg Pathol			2013
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Kanai Y	Single-CpG-resolution methylome analysis identifies clinicopathologically aggressive CpG island methylator phenotype clear cell renal cell carcinomas.	Carcinogenesis	33	1487-1493	2012
Kanai Y	Characteristics of lymph node metastases defining the outcome after radical cystectomy of urothelial bladder carcinoma.	Jpn J Clin Oncol	42	1066-1072	2012
Matsuda J	Involvement of SIK3 in glucose and lipid homeostasis in mice.	PLoS One	7(5)	e37803	2012
山田弘	総説：トキシコゲノミクスとバイオマーカー	日本薬理学雑誌	140	221-225	2012
Yamada H	Identification of a novel set of biomarkers for evaluating phospholipidosis-inducing potential of compounds using rat liver microarray data measured 24-hours after single dose administration	Toxicology	295	1-7	2012

Yamada H	Toxicogenomic multigene biomarker for predicting the future onset of proximal tubular injury in rats	Toxicology	297	47-56	2012
Yamada H	Toxicogenomics discrimination of potential hepatocarcinogenicity of non-genotoxic compounds in rat liver	J. Appl. Toxicol.	Online public ation		2012
Yamada H	Evaluation of DNA microarray results in the Toxicogenomics Project (TGP) consortium in Japan	J. Toxicol. Sci.	37	791-801	2012
山田弘	光毒性試験代替法の第三者評価報告 評価対象：酵母光生育阻害試験と赤血球光溶血試験の組み合わせ	AATEX-JaCVAM	J1(1)	45-87	2012
Mizuguchi K	Inhibitory roles of signal transducer and activator of transcription 3 in antitumor immunity during carcinogen-induced lung tumorigenesis	Cancer Research	72(12)	1-10	2012
Mizuguchi K	Identification and classification of bacterial Type III toxin-antitoxin systems encoded in chromosomal and plasmid genomes	Nucleic Acids Research	40(13)	6158-73	2012
Mizuguchi K	Proteomic Analysis of Hepatitis C Virus (HCV) Core Protein Transfection and Host Regulator PA28gamma Knockout in HCV Pathogenesis: A Network-Based Study	J Proteome Res	11(7)	3664-79	2012
Mizuguchi K	Computational design, construction, and characterization of a set of specificity determining residues in protein-protein interactions	Proteins	80(10)	2426-36	2012
Mizuguchi K	An Open Framework for Extensible Multi-Stage Bioinformatics Software	(proceedings of the 7th International Conference on Pattern Recognition in Bioinformatics (PRIB) 2012) Lecture Notes in Bioinformatics (LNBI)	7632	106-117	2012
Mizuguchi K	Sagace: A web-based search engine for biomedical databases in Japan	BMC Research Notes	31;5(1)	604	2012
Mizuguchi K	A combined proteomics and computational approach provides a better understanding of Hepatitis C virus-induced liver disease	Expert Reviews of Proteomics	9(5)	493-496	2012

Sakate R	A Network of Bioresource Facilities in Japan - The Human Bioresource Consortium Technical Chapter (Japanese Association of Human Bioresource Research)	Biopreservation and Biobanking	11(1)	57-63	2013
Sakate R	Sagace: A web-based search engine for biomedical databases in Japan	BMC Research Notes	5	604	2012
Sakate R	Evolutionary growth process of highly conserved sequences in vertebrate genomes	Gene	504(1)	1-5	2012
Sakate R	Whole-genome sequencing and analysis of the Malaysian cynomolgus macaque (Macaca fascicularis) genome	Genome Biol	13(7)	R58	2012

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BIOBANK PROFILE

A Network of Bioresource Facilities in Japan

The Human Bioresource Consortium Technical Chapter (Japanese Association for Human Bio-Resource Research)

Introduction

RECENTLY, DEMANDS FOR HUMAN SAMPLES have been increasing. As a result, many biobanks have been established throughout the world including in Japan. The increased number of biobanks could benefit from closer communication with each other as well as the the establishment of a network. Although various networks have been established, most of the existing networks are only sharing information on stored samples. Right now, biobanks are exposed to a flood of information evaluating outcomes of biobanking. This demand requires sharing information not only on the availability of stored samples but also on biobank operations and their governance.

Participants

Nine unique bioresource facilities near Tokyo participated in a voluntary study group meeting. Information on each biobank in this network follows.

Current status

This attempt to establish a biobank network is in its infancy as the activities of each biobank are introduced to the group. To solidify this network, the nine facilities made a joint presentation of their activities at the ISBER 2012 meeting in Vancouver[18]. The group plans to meet regularly and strengthen their ties.

Future plan. Our plan is to evaluate various quality assessment methods relevant for a variety of samples, and then provide the methods and references to the participating facilities and to newcomers to the bioresource research community. Eventually, we hope to set up a physical central site to provide timely assistance regarding biobank operations and governance.

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Tel: +81-3-3542-2511 Fax: +81-3-5856-7570

E-mail: kfuruta@ncc.go.jp

Title of Biobank: Chiba University School of Medicine and its affiliated hospitals
Site Location: Chiba Prefecture, Japan
Contact information (Web address, e-mail info and phone for biobank contact):
Fumio Nomura, MD, PhD. E-mail: fnomura@faculty.chiba-u.jp
Kazuyuki Matsushita, MD, PhD. E-mail: kmatsu@faculty.chiba-u.jp
Department of Molecular Diagnosis (F8), Chiba University Graduate School of Medicine, Chiba City, Inohana 1-8-1, Chiba 260-8670, Japan
URL: http://www.ho.chiba-u.ac.jp/en/contents/profile.html
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Hisahiro Matsubara, MD, PhD. E-mail: matsuhm@faculty.chiba-u.jp
Department of Frontier Surgery (M9), Chiba University Graduate School of Medicine, Chiba City, Inohana 1-8-1, Chiba 260-8670, Japan
Tel: +81-43-226-2109, Fax: +81-43-226-2113
URL: http://www.academic-surgery.jp/

Start date of operations: March 1, 2010

Date range of cases: March 1, 2010 to present

Category of biobank: Biospecimens obtained from patients with gastrointestinal, hepatobiliary and pancreatic cancers, and healthy volunteers.

Focus of biobank: Basic/Translational/Epidemiological/Clinical

Major source of funding for biobank: Grants from the Ministry of Education, Culture, Sports, Science & Technology in Japan

Proportional funding sources for biobank:

Institution core budget: 0%
Public targeted donation/foundation: 0%
Grants: 100%
User fees: 0%

Example input statistics:

Overall response to consent: Written informed consent was obtained from each patient 100% of the time prior to surgery

Total individual cases held: Patients with esophageal cancer, approximately 120 cases; colon cancer, approximately 120 cases; stomach cancer, approximately 180 cases.
Percent of cases associated with fresh-frozen tumor biospecimens: 80%
Percent of cases associated with fresh-frozen tumor and blood biospecimens: 60%

Example output statistics:

Biomarker candidates discovered by proteomic studies of biospecimens in our biorepositories during the past 5 years: 10

Publications related to clinical features of gastrointestinal and hepatobiliary malignancy based on our biobank in the past year: 10

What methods are used in your biobank?

Whole blood samples are withdrawn into silica coated plastic venous blood collection tubes (serum: SIM-L1008S; plasma- SPM-K0707E2NA EDTA-2Na with separating agents, mixture of polyolefin hydrocarbon oligomer and silicon dioxide, KYOKUTO Co., Tokyo Japan). The tubes sit for 10 minutes at room temperature, are centrifuged at 1600g for 10 minutes (KUBOTA 5800, KUBOTA, Tokyo, Japan) [1], and the serum samples are aliquoted mannually into 4x1.5mL slim tubes (MS-4702X) (SUMITOMO BAKELITE, CO., Ltd, Tokyo, Japan) at room temperature (20°C) and then stored at −80°C until use.

Between March 1, 2011 and June 30, 2012, peripheral venous blood samples were collected from 1,600 admitted patients using the standard procedures described above. The tumor samples were obtained from tumor epithelium immediately after surgical excision, and corresponding non-tumor epithelial samples were taken 5–10 cm away from the tumor, surgically excised at Chiba University Hospital. All excised tissues were immediately placed in liquid nitrogen and stored at −80°C until analysis.

We have paid particular attention to the effect of time intervals between venipuncture and serum preparation for serum peptidome analyses by MALDI-TOF/MS.[1] Cancer tissues and serum samples were subjected to gel-free and gel-based comprehensive proteome analyses to search for novel biomarkers and therapeutic targets. Furthermore, the establishment of electronic medical records (EMR) or medical care/electronic health records (EHR) was performed to link clinical information to each sample for clinical research. Standardized biobanking of specimens obtained from patients with gastrointestinal and hepatobiliary cancers has allowed us to increase our clinical research, as reported elsewhere.[1–4]

What challenges does your biobank face?

1) Funds are limited. At present, we rely on grants to particular investigators from the Japanese government. We have been requesting financial support from Chiba University Hospital on a regular basis.
2) Not all the medical staff understand the significance and importance of hospital-based biobanking.
3) We are looking at whether to use general or specific informed consent. In other words, samples to meet the investigators' specific requirements vs. samples of potential interest for future use.
4) Linking the clinical data associated with each sample to the repository system.
5) Establishing a network in which multiple tumor banks can share a common database to make collective contributions to meet investigators' requests.

Title of Biobank: Kanagawa Cancer Research and Information Association (KCRIA) Tumor Tissue Center
Site Location: Kanagawa Cancer Center (KCC), Yokohama, Japan
Contact information:
Yasuo Takano, MD, PhD, Director of KCC Research Institute
Tel: +81-45-391-5761 (ext 5105)
E-mail: ytakano@gancen.asahi.yokohama.jp
Yohei Miyagi, MD, PhD, KCC Research Institute
Tel: +81-45-391-5761 (ext 5123)
E-mail: miyagi@gancen.asahi.yokohama.jp
URL: http://kcch.kanagawa-pho.jp/kikou/index.html

Start date of operations: October 2006

Date range of cases: October 2006 to present

Category of biobank: Basic research

Focus of biobank: Basic/Translational/Epidemiological/Clinical

Major source of funding for biobank: members of KCRIA (http://kcch.kanagawa-pho.jp/kikou/index.html), including Kanagawa prefecture, medical schools at Kanagwa prefecture, biomedical & pharmaceutical companies at Kanagwa prefecture.

Proportional funding sources for biobank:

Institution core budget: 97%
Public targeted donation/foundation: 0%
Grants: 2%
User fees: <1%

Example input statistics:

Overall response to consent: 98% Yes (with permission for genome analysis: 85%)

Total individual cases held: 2830 frozen tissues (FFPE tissues from 581 patients, and serums/genome DNAs from 2582 patients)

Cases associated with fresh-frozen tumor biospecimens: Distributed samples were 1856 frozen tissues, 581 FFPE tissues, 1020 genome DNAs and 1724 serums as of January 2012

Example output statistics:

Approximate number of studies supported last year: 9

Approximate number of cases released last year: 345 frozen tissues, FFPE sections from 205 patients, 521 serum

Publications in past year (based on biobank and users): 3

What methods are used in your biobank?

The tumor tissue center is collecting tumor-related samples including frozen tumor tissues, formalin-fixed and paraffin-

embedded (FFPE) tumor tissues, serum from the patients before treatment, and genome DNAs of peripheral white blood cells. Corresponding normal tissues are also collected if possible. Clinical information is annotated to each sample as precisely as possible. We are evaluating the quality of tumor samples by two indices: the RNA Integrity Number (RIN) of extracted total RNAs from randomly chosen frozen tissues examined with the 2100 Bioanalizer (Agilent Technologies, Inc., Santa Clara, CA); and histopathological examination of parts of all frozen tissues prepared in the Optimal Cutting Temperature (OTC) compound and evaluation of the contents of tumor cells.

What challenges does your biobank face?
Almost 6 years have passed since the establishment of the KCIRA Tumor Tissue Center, and two major problems appeared. One is due to the economic depression of the prefecture and the other is due to the progress of cancer research technologies and demand for raising the quality of specimens. At present, almost all the working expenses are paid by KCC, and the income of the tumor tissue center is almost negligible. Under this situation, it is difficult to increase the working expenses, and therefore difficult to increase the number of personnel. We need at least one more laboratory technologist and two more research nurses to raise the quality of samples and annotated clinical information, and to take informed consents from the patients.
At present, we keep excised organs in a refrigerator for one to two hours before sampling. Although this method maintains RIN between 6 and 8, many parameters may have changed from their original state, not only in the amount and profile of mRNAs and proteins expressed, but also in the modifications of nucleic acids and proteins. This may also influence the results from upcoming technologies. To establish a tumor tissue center with a higher quality of sample, annotated clinical information, and process informed consent, a stable increase in working expenses, such as national funding, is needed. Establishment of tumor tissue banks funded by the national budget at several cancer centers could increase the numbers of samples collected under the same quality control procedures and could promote more cancer research.

Title of Biobank: Yokohama City University Advanced Medical Research Center Biobank

Site Location: Yokohama City University Advanced Medical Research Center, Kanazawa-ku, Yokohama, Japan

Contact information:
Sentanbb@yokohama-cu.ac.jp
phone. +81 45 787 2733

Start date of operations: April 1, 2007

Date range of cases: 2007–present

Category of biobank: Surgery, Urology, Gynecology, Neurosurgery and Orthopedic

Focus of biobank: Translational research

Major source of funding for biobank:
Grants in aid from the Ministry of Education, Culture, Sports, Science and Technology

Proportional funding sources for biobank:

Institution core budget:	2.5%
Public targeted donation/foundation:	5%
Grants:	92.5%
User fees:	None

Example input statistics:

Overall response to consent: Yes 52%, No and Unknown 48%

Total individual cases held: 1202

Cases associated with fresh-frozen tumor biospecimens: 1179

Example output statistics:

Approximate number of studies supported last year: 3 projects

Approximate number of cases released last year: 106 cases

Publications in past year (based on biobank and users): 2 publications

What methods are used in your biobank?
Using appropriate informed consent, the biobank is collecting human samples from healthy volunteers and the patients of our university hospital. The samples are mainly human tissues obtained at surgical operation, most of which are from cancer patients. Human tissues resected at surgery must be evaluated by the pathologists to determine future clinical management, especially in cancer patients. Thus, sampling from human tissues must be conducted carefully so as to not disturb the pathological examination. Specimens for the biobank must be freshly collected before the pathological examination. The samples are cut from the resected tissue by board eligible pathologists who engage in the pathological examination in our University Hospital. The pathologists determine the suitable sampling method for the biobank. We consider this the most important step for appropriate sampling for further research.

What challenges does your biobank face?
We have many issues to resolve and overcome for the promotion of the biobank. We do not have constant financial support. The biobank has been supported by a seven year grant from the government. The most urgent issue is how to obtain constant financial support. Another is the promotion of use of the biobanked samples. Currently, most clinical departments in our medical school store their own human tissue samples in addition to the biobank's sample collection. Thus, they use their own samples for research instead of the biobank samples. Further understanding of what the biobank has to offer may resolve this problem and could provide assurance about the integrity of the tissue samples to be used in research.

Title of Biobank: Chiba Cancer Center (CCC) Biobank

Site Location: 666-2 Nitona, Chuo-ku, Chiba, Chiba 260-8717, Japan

Contact information:
Takehiko Kamijo: tkamijo@chiba-cc.jp

Akira Nakagawara: akiranak@chiba-cc.jp
Phone: +81-43-264-5431
URL: http://www.chiba-cc.jp/inst/eng/intro.html

Start date of operations:: 1996

Date range of cases: 1996–present

Category of biobank: Adult and pediatric (mainly neuroblastoma and hepatoblastoma) cancers

Focus of biobank: Basic/Translational/Epidemiological/Clinical

Major source of funding for biobank: Institution core budget

Proportional funding sources for biobank:
Institution core budget: 80%
Public targeted donation/foundation: 5%
Grants: 15%
User fees: 0%

Example input statistics:
Overall response to consent: nearly 99% Yes

Total individual cases held: 8,800 adult and 2,800 pediatric samples from cancer patients (the latter has been known as one of the world's major neuroblastoma tissue banks)

Example output statistics:
Approximate number of studies supported last year: 4 adult cancers; 20 pediatric cancers

Publications in past year (based on biobank and users): Since the biobank's inception: more than 240

What methods are used in your biobank?
DNAs and RNAs are routinely prepared from frozen tissues, and the quality is subsequently checked. These materials, which are securely stored in constantly- monitored freezers, have been used for state-of-the-art molecular diagnosis to determine therapeutic strategies and for basic and translational research projects upon the ethical committee's approval. The amount of sample to be used for research is separately qualified by a CCC Biobank committee.

Since establishment of the CCC Biobank in 1996, more than 240 scientific articles and reviews about pediatric cancers have been published, especially reports of neuroblastoma, the second most common pediatric solid malignant tumor derived from the sympathetic nervous system. Several retrospective studies have revealed that molecular signatures are strongly correlated with patient prognoses which has led to the construction of new risk stratification systems.[5–9] Of note, anaplastic lymphoma kinase (ALK) is mutated in 6–9% of sporadic cases, and is either amplified or constitutively activated through mutations mainly within the kinase domain, promoting the possibility of new therapeutic strategies using ALK inhibitors. Additional candidates for outcome prediction such as the methylation phenotype of tumor DNA and expression profiles of non-coding RNA have also been proposed.[10] Such a variety of information will help us understand the heterogeneity of neuroblastoma biology, and further, the combined use of the signatures will be beneficial in predicting prognosis with high accuracy, as well as choosing a suitable therapy for the individual patient.

Title of Biobank: The Tsukuba Human Tissue Biobank (THB), in the University of Tsukuba Hospital

Site Location: University of Tsukuba Hospital, Ibaraki Prefecture, Japan

Contact information (Web address, e-mail info and phone for biobank contact):
URL: http://www.s.hosp.tsukuba.ac.jp/thdc/ (available only in Japanese)
Tel: +81 29 853 3715
E-mail: trrc@hosp.tsukuba.ac.jp

Start date of operations: April 2009

Date range of cases: April 2009–present

Category of biobank: Colon, liver, pancreas breast, and lung

Focus of biobank: Basic/Translational/Clinical

Major source of funding for biobank: Ministry of Education, Culture, Sports, Science and Technology

Proportional funding sources for biobank:
Institution core budget: 90%
Grants: 10%

Example input statistics:
Overall response to consent: 100% Yes

Total individual cases held: 550 (321 lung cancers; 117 colon cancers; 89 liver cancers; 9 pancreatic cancers; and 15 breast cancers)

Cases associated with fresh-frozen tumor biospecimens: 100%

What methods are used in your biobank?
We manage more than 150 items of patient clinical information, including patient history, family history, and medication history. Medical technologists and research assistants perform banking of the specimens. Surgical specimens are divided into small fractions and immediately put into vials. All specimens are stored in the ultra-low freezer within 30 minutes after receipt. In THB, a research coordinator works with the doctor to obtain informed consent. We have our own consent form which is designed to be flexible in case of revision of the ethical guidelines.

To improve the administrative system in THB, we organized three internal committees (steering committee, research review board, and ethical review board) and one external evaluation committee. The steering committee consists of 12 members affiliated with the University of Tsukuba, and important decisions regarding THB are taken by this committee. The research review board and the

ethical review board review research plan applications. These committees consist of experts, such as scientists, biologists, clinicians, and ethicists from various fields. The external evaluation committee consists of 4 members (legal expert, medical doctor, pharmacist, and scientist) which give advice to THB.

What challenges does your biobank face?
The system that provides samples is currently not working because of an insufficient number of samples. In the future, we would like to collect many types of specimens from other hospitals in order to fulfill the various requests of researchers. As a first step, we have established the facilities and infrastructure required for operation. Next, we plan to establish practical collaborations with other hospitals in the surrounding area. The University of Tsukuba Hospital, to which THB belongs, has already built a cooperative relationship with the local hospital for pathological diagnosis.

Title of Biobank: Autopsy Tissue Bank of TMGH-Autopsy Resource

Site Location: Tokyo Metropolitan Geriatric Hospital (TMGH), Tokyo, Japan

Contact information
URL: http://www1.tmghig.jp/biobank/index.html (in Japanese)
Tel: +81-3-3964-1141 ext. 2285
E-mail: centpath@tmig.or.jp
Contacts: Dr. Tomio Arai, Bioresource Center for Geriatric Research (BRCGR), TMGH

Start date of operations: April, 2010

Date range of cases: 2010–present

Category of biobank: Basic and clinical research tissue bank

Focus of biobank, primary: Basic/Translational/Clinical

Membership of biobanks (networks, affiliations): Human Bio-resource Consortium Technical Chapter, Japan

Major source of funding for biobank: Institutional core budget

Proportional funding sources for biobank:
Institution core budget: 90%
Public targeted donation/foundation: 0%
Grants: 5%
User fees: 5%

Example input statistics:
Overall response to consent (Yes/No/Unknown %): 90%/10%/0%

Total individual cases held:
41 cases (30–35 tissues in each case)
Cases associated with fresh-frozen tissues: 100%
Cases associated with fresh-frozen tissues and serum samples: 80%

Example output statistics:
Approximate number of studies supported last year: 0
Approximate number of cases released last year: 0
Publications in past year (based on biobank and users): 0

What methods are used in your biobank?
The bereaved family is asked to participate in the tissue bank project prior to autopsy. We take 2 cm-sized cubes of tissue samples from 30 to 35 various organs at autopsy, cut into 5 mm-sized cubes and stored in −80°C freezers. The sampled organs include left ventricle and left auricle of heart, ascending aorta, inferior vena cava, trachea, larynx, peripheral lung, esophagus, submandibular gland, liver, gallbladder, pancreas, renal cortex and medulla, ureter, prostate, uterine cervix and body, testis or ovary, female breast, pituitary gland, thyroid, parathyroid, adrenal gland, bone marrow, lymph node, spleen, skin, mesenteric and subcutaneous fat, brachial nerve, quadriceps muscle, diaphragm, lumbar vertebra, costal cartilage, and intervertebral disc. These tissues are distributed essentially free of charge to the researchers after review by a research committee and approval by an ethical committee. The characteristic feature of this tissue bank is normal tissue of various organs.

What challenges does your biobank face?

- Ensuring continued financial support for the biobank;
- Implementing a public relations campaign;
- Ensuring quality control of the samples; and
- Setting up national and international networks.

Title of Biobank: Collaborating Project of TMGH-Autopsy Resource

Site Location: Tokyo Metropolitan Geriatric Hospital (TMGH), Tokyo, Japan

Contact information
URL: http://www.tmghig.jp/pathology-d/index.html (in Japanese)
Tel: +81-3-3964-1141 ext. 2285
E-mail: centpath@tmig.or.jp
Contact: Dr. Tomio Arai, Bioresource Center for Geriatric Research (BRCGR), TMGH

Start date of operations: January, 2009

Date range of cases: 2009–present

Category of biobank: Basic and clinical research tissue bank

Focus of biobank, primary: Basic/Translational/Clinical

Membership of biobanks (networks, affiliations): Human Bio-resource Consortium Technical Chapter, Japan

Major source of funding for biobank: Institutional core budget

Proportional funding sources for biobank:
Institution core budget: 90%
Public targeted donation/foundation: 0%
Grants: 5%
User fees: 0%

Example input statistics:
Overall response to consent (Yes/No/Unknown %): 100% of autopsy cases

Total individual cases held: 2,500 cases (frozen tissues, serum and DNA)

Cases associated with fresh-frozen tissues: 100%
Cases associated with fresh-frozen tissues and serum samples: 80%

Example output statistics:
Approximate number of studies supported last year: 19
Approximate number of cases released last year: 2,000
Publications in past year (based on biobank and users): 11

What methods are used in your biobank?
The Collaborating Project has started to promote the use of all autopsy materials and information derived from the TMGH-Autopsy Resource (TMGH-AR) since 2009. No medicolegal autopsy is included. The average age at death of the patients is 80 years and male to female ratio is approximately 1:2. Since 1972, all clinical and pathological information from more than 7,600 cases has been stored and kept updated in a database called ANATOMY.[11] We have also developed a geriatric autopsy database for molecular epidemiological studies on more than 2,500 cases, which contains histories of smoking and drinking, clinical diagnosis including 26 geriatric diseases, serum lipid data, 750 pathological findings, 42 major pathological diagnosis, atherosclerotic degrees of 10 major arteries, and emphysematous degrees.[12] We have started storing serum taken before death since 1995, with more than 2,000 serum samples currently available. Tissues from kidney, liver, heart and lung (or esophagus) have been kept frozen in deep freezers in all cases since 1995, and DNA has been extracted from unfixed renal tissue (2,500 cases) or from paraffin sections (5,200 cases).

What challenges does your biobank face?

- Ensuring continued financial support for the biobank;
- Implementing a public relations campaign;
- Ensuring quality control of the samples; and
- Setting up national and international networks.

Title of biobank: Rare Disease Bank of the Ministry of Health, Labour, and Welfare, Japan

Site Location: National Institute of Biomedical Innovation, Osaka, Japan

Contact information:
URL: http://raredis.nibio.go.jp/
Tel: +81 72 641 9019
E-mail: raredis-office@nibio.go.jp
Contacts: Dr. Ichiro Takahashi (Director), Dr. Ryuichi Sakate, Dr. Tohru Masui

Start date of operations :
April, 2009

Date range of cases :
2009–present

Category of biobank:
Human biospecimen of rare diseases

Primary research focus of biobank:
Basic/Translational

Major source of funding for biobank:
Institution core budget

Proportional funding sources for biobank:
Institution core budget: 90%
Public targeted donation/foundation: 0%
Grants: 10%
User fees: <1%

Example input statistics:
Overall response to consent (Yes/No/Unknown %): N/A (consents are handled by collaborating institutions)
Total individual cases held: 205 for 39 diseases (Genomic DNA from 111 patients, plasma/serum from 158 patients, and cells from 56 patients as of June 2012 - some of these are not ready to be released.)

Example output statistics:
Approximate # of studies supported last year: N/A (just started to release this year)
Approximate # of cases released last year: N/A (just started to release this year)
Publications in past year (based on biobank and users): 4

What methods are used in your biobank?
The Rare Disease Bank was established in National Institute of Biomedical Innovation (NIBIO) by the Ministry of Health, Labour, and Welfare, Japan (MHLW) in 2009. The objective of the bank is to centralize and impartially distribute rare disease specimens with quality control in order to promote research on rare diseases. Specimens are collected in collaboration with the MHLW's research projects to overcome intractable diseases (130 projects). An institutional review board (IRB) was instituted at NIBIO to exclusively serve the bank reviews prior to collection/distribution of specimens.
The bank started distributing specimens to researchers in October 2011. The bank can currently distribute genomic DNA, serum and plasma from patients with 14 diseases (e.g., HTLV-1-associated myelopathy[13], Kennedy disease[14], Primary aldosteronism[15]). Information regarding distribution of specimens is available from the Rare Disease Bank website (http://raredis.nibio.go.jp/, currently in Japanese only). In order to obtain detailed information on the specimens and apply for distribution, users must be registered.

What challenges does your biobank face?
The Rare Disease Bank is managed based on "Ethical Guidelines Regarding Human Genome and Genetic Analysis Research" (Ministry of Education, Culture, Sports, Science and Technology, MHLW, and Ministry of Economy, Trade and Industry). Under the guidelines, human specimens should be distributed from biobanks in an unlinked and anonymizedmanner. In line with this, neither the bank nor the specimen-collection group should handle inquiries from researchers regarding the specimens after distribution. However, it is sometimes important to distribute further clinical information on specimens to researchers, while conveying their inquiries to clinical doctors.

Title of Biobank: National Cancer Center Hospital Biobank

Site Location:
Division of Clinical Laboratories
National Cancer Center Hospital (NCCH)
5-1-1, Tsukji, Chuo-ku, Tokyo, 104-0045 JAPAN
Tel: +81-3-3542-2511 Fax: +81-3-5856-7570

Contact information
Koh Furuta
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Tel: +81-3-3542-2511
Fax: +81-3-5856-7570

Start date of operations:
October, 2002

Date range of cases:
January 1st, 2006 to present. Samples collected during October 2002 to December 2005 were discarded. Storage duration is for five years.

Category of biobank:
Basic research

Focus of biobank:
Mainly clinical, partially translational research

Major source of funding for biobank:
Hospital budget and grant from government (the Ministry of Health and Labour).

Proportional funding sources for biobank:
Institution core budget: 40%
Public targeted donation/foundation: 0%
Grants: 60%
User fees: 0%

Example input statistics:
Overall response to consent (Yes/No/Unknown %): 90% Yes /less than 1% No/ 9% Unkown

Total individual cases held: Approximately 650,000 samples of plasma or serum.

Cases associated with fresh-frozen tumor biospecimens: None. This particular biobank is for bio-fluids, mainly blood.

Example output statistics:
Approximate number of studies supported last year: 14.
Approximate number of cases released last year: 3084 samples.
Publications in past year (based on biobank and users): 5.

What methods are used in your biobank?
Two technicians and one doctor are the working force in this NCCH-Biobank. Stored samples are mainly blood, such as plasma and serum. In addition, buffycoat, DNA, and RNA are collected, although in small numbers. Blood samples are stored at −20°C using regular cryotubes. Samples collected before September 2011 are stored in 5 ml cryotubes. Samples collected after that time are stored in 1 ml 2D barcoded cryotubes. The NCCH provides a broad opt-in consent format to the patients for the purpose of utilization of samples for other than their own medical necessities. Institutional Review Board approval is mandatory for use of the samples. Currently in-hospital doctors and researchers, including outside personnel under collaboration with in-hospital personnel, can apply for sample utilization.

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BMC Research Notes

TECHNICAL NOTE Open Access

Sagace: A web-based search engine for biomedical databases in Japan

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Abstract

Background: In the big data era, biomedical research continues to generate a large amount of data, and the generated information is often stored in a database and made publicly available. Although combining data from multiple databases should accelerate further studies, the current number of life sciences databases is too large to grasp features and contents of each database.

Findings: We have developed Sagace, a web-based search engine that enables users to retrieve information from a range of biological databases (such as gene expression profiles and proteomics data) and biological resource banks (such as mouse models of disease and cell lines). With Sagace, users can search more than 300 databases in Japan. Sagace offers features tailored to biomedical research, including manually tuned ranking, a faceted navigation to refine search results, and rich snippets constructed with retrieved metadata for each database entry.

Conclusions: Sagace will be valuable for experts who are involved in biomedical research and drug development in both academia and industry. Sagace is freely available at http://sagace.nibio.go.jp/en/.

Keywords: Search engine, Biomedical data, Biomedical resources, Faceted search, Microdata

Findings

Modern biomedical research produces increasing amounts of data, much of which is stored in numerous public databases. (Some of these databases are described in the Database Issue of Nucleic Acids Research each year [1]). As life sciences become ever more data-driven, there is great potential for mining multiple different databases and generating a new knowledge. The sheer number of databases, however, makes data integration a formidable task.

To tackle this issue, the Database Center for Life Science (DBCLS; [2]) and the National Bioscience Database Center (NBDC; [3]) were established in Japan in 2007 and 2011, respectively, with the mandate to archive and integrate Japan's life sciences databases. In an effort to promote effective data integration, they compiled a database list and developed a framework for distributed search systems, based on which, designated national centers can create domain-specific search websites. The indexes for the selected databases were created by NBDC and other designated national centers, including the National Institute of Biomedical Innovation (NIBIO; [4]).

In close collaboration with the DBCLS and the NBDC, we at the NIBIO have developed a search web site called 'Sagace' (Figure 1), as a first step towards efficient integration and retrieval of biomedical data from online public databases. This search web site has been customized to search more than 300 biomedical databases in Japan, containing biological data such as gene expression and proteomics data, and biological resources such as mouse disease models and human cultured cells. Our aim is to build a search web site that can assist quick and accurate data retrieval. Here, we describe technical aspects and usage examples of 'Sagace'.

Features of Sagace

The core search engine of Sagace is a full-text search system, which searches for user-supplied query terms in all stored documents, similar to current popular search engines such as Google and Yahoo!. However, these general-purpose search engines often fail to retrieve

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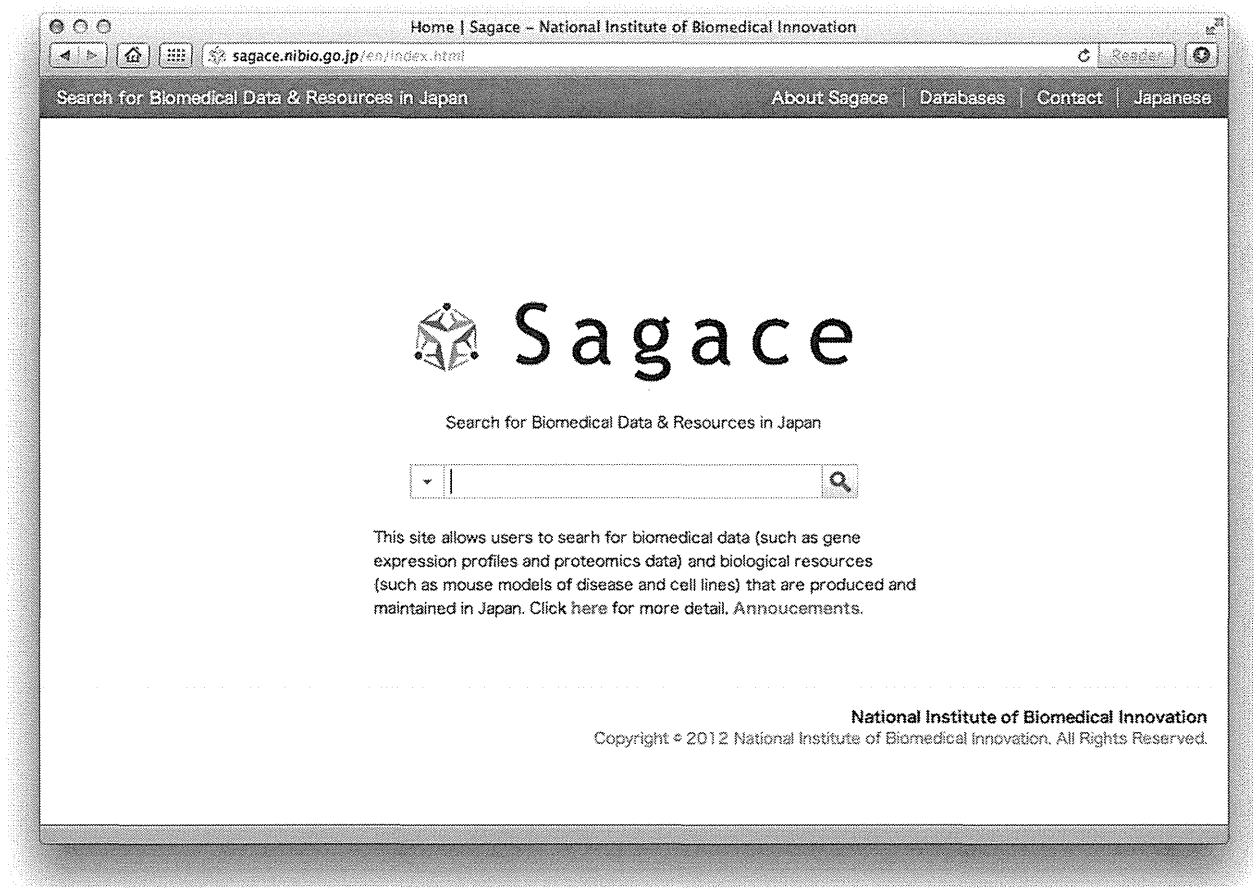

Figure 1 The top page of Sagace. Sagace can be freely accessed at http://sagace.nibio.go.jp/en/.

relevant biological data, because, unlike standard web pages, specialist biological databases tend to provide only short natural language descriptions for the individual entries. General-purpose search engines typically rank search results according to the number of matched query terms in each stored document (with adjustments based on the frequency distribution of query terms in the document collection). Therefore, documents with short text are ranked low by standard document retrieval systems. Even if a search engine retrieves entries from a biological database, the user often finds it difficult to judge their relevance, because of the lack of textual information. To address these issues, we implemented three features in Sagace: i) manually assigned weights to the crawled databases for improving the ranking system, ii) a faceted system to refine the search results effectively, and iii) rich snippets to show informative metadata for databases.

First, we have introduced a system that modifies the order of search results according to the weights assigned to individual databases. We have examined manually all the (>300) crawled databases and assigned two different weights. The higher weight has been assigned to the databases that are relevant to human disease and drug discovery. Thus, plant and bacterial databases have tended to be (but not always) assigned the lower weight. We have also assigned the lower weight to many of the reference-type databases such as biological term dictionaries and patent databases, since these databases are likely to be ranked high (irrespective of their content) in the full-text search engine adopted by Sagace (see below). Because the current weights were defined subjectively and thus difficult to evaluate, we plan to optimize the weights by using a more automatic method, for examples, based on the access log data.

Second, to assist in improving search results, we implemented a faceted system. It was reported that users tend to use filters to narrow down the search results and change the queries *after the search*, rather than configuring search engine parameters *before the search* [5]. Therefore, in Sagace, we implemented a faceted system to narrow down the search results [6]. We examined and classified all the crawled databases from three different points of view: 1) the content type (e.g., biological

resources, protocols, and references), 2) the species of organism that each database covers, and 3) the level of organization (e.g., genome and gene, cell and tissue, and organism). Using these three categories, users can apply multiple filters and refine their search results effectively. In Sagace, users can use the three facet categories displayed on the left of the search results (Figure 2).

Last, we implemented in Sagace snippets and rich snippets, the few lines of text that appear under each search result, to provide users with condensed information about the retrieved page (Figure 2). Generally, the snippet for a page includes its summary description, while the rich snippet shows page metadata. To create rich snippets for entries from biological databases, Sagace retrieves the metadata for each database entry page, if they are stored in the microdata format [7].

Recently, several metadata formats for web pages have been proposed, such as RDFa [8], microformats [9], and microdata [7]. Among these, we have decided to use microdata, because it was adopted by schema.org [10], a collection of schemas for structured data markup on web pages, proposed by three major search engines (Google, Yahoo! and Microsoft) [11-13]. The vocabulary on schema.org provides an unambiguous description of data attributes such as the name of the item, the URL, the creation date, the last modification date, keywords and the provider name. However, there was no adequate vocabulary set on schema.org for biological databases and therefore, we have proposed an extension to the schema.org vocabulary [14]. Attributes specific to biological database entries can now be described, including the entry identifier, the database name to which the entry belongs and the taxonomy identifier of the entry. When our extension is officially approved and as long as the database providers specify these attributes in the given format, search engine crawlers will recognize the meaning of these attributes and retrieve the relevant information. As an example, we introduce searching with

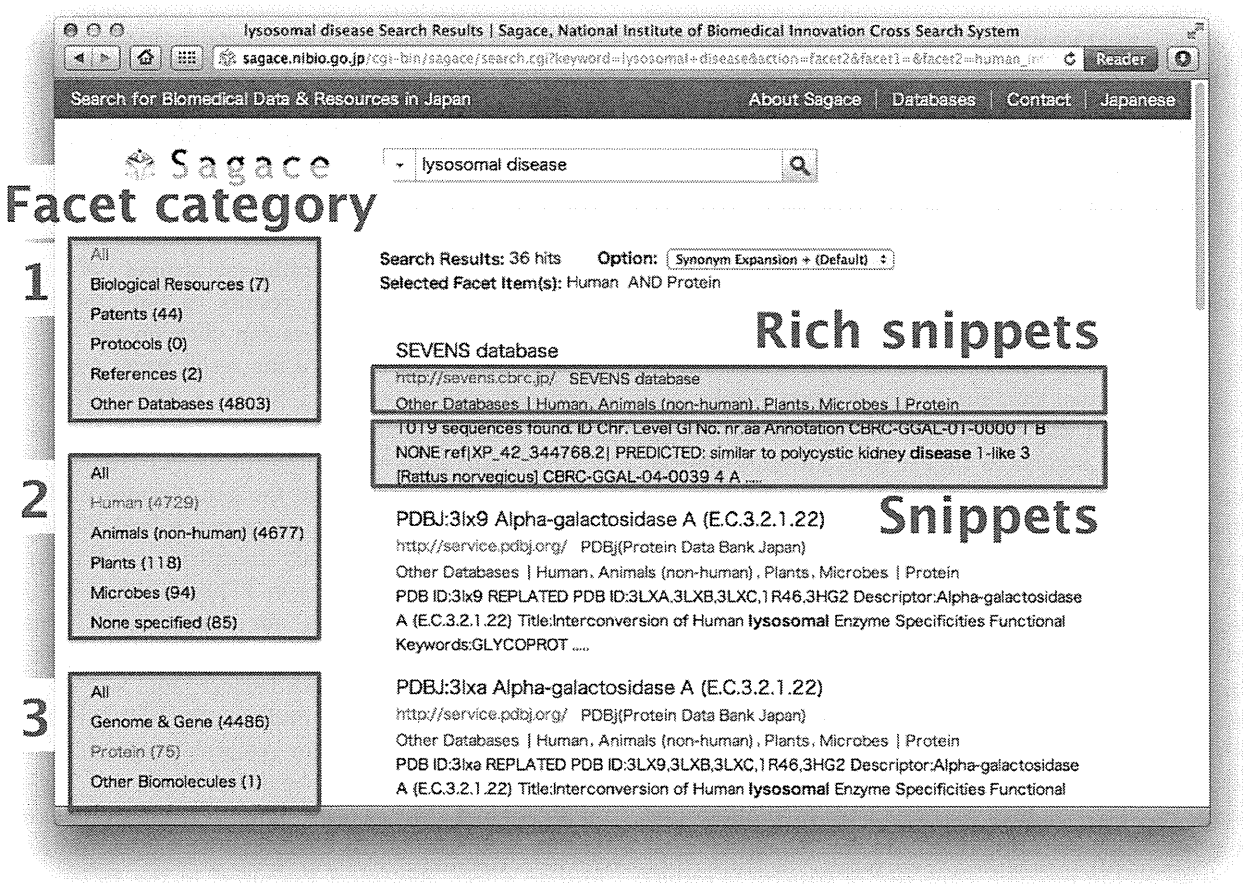

Figure 2 The search result page of Sagace. Summary information (in the form of snippets and rich snippets) about each search result helps users judge the relevance of the search result. When the number of search results is large, the users can refine their search results with three types of facet categories on the left column. Combining more than one facet categories refines the search results further. The users can also refine the search results using information in the rich snippets, such as the database name and the species.

an entry identifier. By adding a "[id]" tag after the query term, users can directly search for a specific database entry with the specified identifier. Currently, only a few of the crawled databases offer the entry ID field but since the schema.org extension that we propose contains "entryID" in its data structure, this approach will work more efficiently over time when the schema.org extension becomes widely adopted by database providers.

Currently, only the Japanese Collection of Research Bioresources (JCRB) Cell Bank [15] has officially employed our proposed vocabulary but we expect the importance of our proposal to be recognized more widely, since providing structured information is the best way to organize and integrate a large number of databases. With more databases adopting this vocabulary set, metadata for biological databases should provide not only better search experiences but also novel applications. For instance, by collecting microdata for biological databases in a systematic manner, a catalogue of biological databases can be constructed automatically. It would also be possible to develop script libraries that utilize microdata information, such as those for Google Maps [16]. For example, a library can be written to obtain the species information from a database entry and display the corresponding 'Taxonomy icon' [17], which is a graphical image representing each species.

Sagace is similar to other cross-database search systems such as Entrez [18,19] at the National Center for Biotechnology Information (NCBI) and EB-eye [20,21] at the European Bioinformatics Institute (EBI). While Entrez allows users to search not only indexed text but also any value in the data (including sequences and numerical counts), EB-eye focuses on an indexed collection of selected textual content (such as gene names and descriptions). In this sense, Sagace, as a textual search engine, is more similar to EB-eye than Entrez. However, unlike Entrez and EB-eye, which navigate through the databases hosted by NCBI and EBI, respectively, Sagace searches a wide collection of biomedical database on the web (including small and specialist databases). This characteristic makes the range of Sagace users more diverse than those of the two other search engines. It requires the search interface to meet wider demands of users and to adapt to unscheduled format changes in the crawled databases. It is these factors, while making search results of Sagace less structured than those of Entrez and EB-eye, that motivated us to propose and promote the schema.org extension for biological databases; we aim to produce some sort of structured results with a minimal effort from database providers. Besides, the faceted search allows to narrow down the search results from various aspects, and the rich snippets help users to grasp quickly a summary of each entry.

Implementation

We employed Hyper Estraier [22] as a core search engine to construct our search system. Hyper Estraier is an open source full-text search engine equipped with all basic features of full-text search as well as multilingual support. Hyper Estraier also utilizes a Peer-to-Peer (P2P) distributed search technology to build large-scale search applications. Multiple organizations can take charge of crawling different databases, and the resulting inverted index files can be shared. We collaborate with the NBDC and maintain our crawling system together. The NBDC sets up its own search engine [23], and both our search engines access the common inverted index files on the fly. Sagace, however, assigns weights to a selected subset of the databases, as described above, and thus, search results can be different between the two search engines.

Example usage

We present two usage examples of Sagace: one to collect information about a specific gene, and the other to find distributors of particular cultured cells.

In 2001, Eisenberg et al. identified GNE (the gene encoding bifunctional UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase) as the causal gene for Distal Myopathy with Rimmed Vacuoles [24]. As shown in the gene product name, GNE is a fusion gene of two enzymes and has two distinct functions. Querying Sagace with the full name of this gene product "bifunctional UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase" produces around 40 search results. To restrict search results to only those from gene-related databases, users can click on the 'Genome & Gene' facet on the left of the result page. Among the restricted search results, a hit to a KEGG [25] entry shows that this gene is the causal gene for another disease named 'Sialuria'. Another hit to FLJ Human cDNA Database [26] indicates that the gene locates on human chromosome 9. Moreover, other pages lead the user to multiple three-dimensional structures of human N-acetylmannosamine kinases in PDBj [27], known single nucleotide polymorphisms for the queried gene in GeMDBJ [28], and protein-protein interaction information in the Genome Network Project [29].

A second example is to find specific Induced Pluripotent Stem (iPS) cells [30] for research purposes. A number of search results will be returned by a query with "iPS". Adding a query term "lung" will reduce the search results dramatically. To narrow down the search results further, select 'Biological Resource' in the facet categories at the upper left column of the page. If necessary, the list may be narrowed down further by selecting 'Human' in the facet categories at the lower left column. From the refined list of search results, the user can easily

find the required cell type (e.g., human lung fibroblast-derived iPS cells), along with the distributor details.

Availability and requirements

Project name: Sagace.

Project home page: http://sagace.nibio.go.jp/en/.

Computer system requirements: Any operating system with any modern web browser.

Any restrictions to use by non-academics: None.

Abbreviations

DBCLS: Database Center for Life Science; GNE: The gene encoding bifunctional UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase; iPS cell: Induced Pluripotent Stem cell; NBDC: National Bioscience Database Center; NIBIO: National Institute of Biomedical Innovation.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MM designed the web interface. MM, YI, YC, CN, RS, and KM selected and ranked the crawled databases. RS, YS, and TM provided data for the NIBIO databases. All authors tested and contributed to the user interface. YI, MI and KM participated in developing the website. MM and YI wrote the manuscript. KM supervised the project and assisted in the editing of the manuscript. All authors read and approved the submitted manuscript.

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