＜使用培地に関して＞

ご提供しております細胞の培地・添加物のメーカー・品番等に関しましては、下記ホームページにてご確認下さい。

http://www.brc.riken.jp/lab/cell/rcb/med_table.shtml

尚、血清(FBS)のメーカー・Lot に関しましては、当バンクで使用中のものをお答えすることは可能ですが、当バンクより分譲してはおりませんので、ご了承下さい。

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ご購入いただいた細胞の、融解操作を含めた培養方法に関しましては、ホームページの下記サイトをご参照下さい。

http://www.brc.riken.jp/lab/cell/manual/

＜培養条件に関して＞

各細胞の培養条件に関しましては、それぞれのデータ画面をご参照下さい。また、当細胞バンクでは原則として寄託時の条件で培養を行っており、それ以外の条件での増殖能等の確認は行っておりません。従いまして、他の培地で培養する場合は、必要量だけ実験用培地で培養し、残りの細胞は維持用培地で培養することをお勧め致します。

補足:申込書記入方法およびオンライン入力

1. 申込書類の記入方法

一般細胞(RCB)の書式の記入方法です。

・ 細胞材料提供依頼書(書式 C-0001)

RIKEN BRC CELL BANK

(書式 C-0001-1)

細胞材料提供依頼書

年　月　日

独立行政法人理化学研究所 バイオリソースセンター
細胞材料開発室 御中

下記の細胞を提供願います。提供にあたって別紙提供同意書記載項目を遵守します。
支払い方法は（**公費・校費、科研費、その他**）です。

依頼者氏名	送付先氏名
(英名)	(英名)
職名	E-mail
E-mail	
所属機関	
研究課題名	
住所 〒	
TEL	FAX

No.	細胞材料名	アンプル数	Restriction

細胞材料開発室からの発送日は
□ 特に指定しません。
□ 月 日(火曜日)に願います。

すでにMTAを締結している場合: 提供同意書 (MTA) No. RM

研究課題名:

特記事項があれば

支払い方法が決まっている場合は、○をつけて下さい。
依頼者と異なる場合はご記入下さい。
生物資源同意書の「利用者」と同じ方をご記入下さい。
各リソースの「Restriction」の記号をご記入下さい。
発送日の指定がある場合はご記入下さい。その場合は、発送予定表より選択して下さい。発送日は、こちらからお知らせいたします。ご希望に添えない場合もございますがご了承下さい。
すでにMTAを締結している場合はご記入下さい。
この依頼書1部とこの同意書2部は、必ず郵送して下さい。FAXでは送らないで下さい。

****

* 「生物遺伝資源提供同意書」2部を郵送して下さい。到着後、正式受付となります。ただし、上記のMTAとリソース名、課題名、利用者(機関・会社名、住所、研究責任者、機関長)が同一であれば提出の必要はございません。

** Restrictionが b または c の細胞は「提供承諾書」を添えてお申込下さい。

*** 「遺伝子組換え生物等の使用等の規制による生物の多様性の確保に関する法律」に該当する遺伝子組換え生物の場合は、(1)遺伝子組換え生物実験の実験承認番号 (2)課題名 (3)研究責任者 (4)承認

****

〒305-0074 茨城県つくば市高野台3-1-1
独立行政法人理化学研究所

(受付日　　年　月　日)
(受付番号　　　　　)

・ 細胞材料提供承諾書(書式 C-0002)

20070507

RIKEN BRC CELL BANK

(書式 C-0002)

細胞材料提供承諾書

申込日　　　年　　月　　日

独立行政法人理化学研究所　バイオリソースセンター
細胞材料開発室　御中

生物遺伝資源同意書と同じ記載をして下さい。

<<利用者>>
住所：〒
機関名・会社名：
機関長：
研究責任者：
担当者：
E-mail：
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利用者は、下記の条件で寄託者から提供承諾を受けたことを理研BRCに報告します。

記

課題名（生物遺伝資源提供同意書と同一内容でご記入下さい。）

リソース名（No.）

同一の提供条件の場合は、この書式で複数の細胞材料の承諾を得ることができます。

提供条件（カタログ及びホームページに掲載された条件をご記入下さい。）

カタログ、ホームページに記載された提供条件を文言でご記入下さい。

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寄託者は、上記の条件で利用者への提供を承諾いたします。
住所：〒
機関名・会社名：
研究責任者：
担当者：

申込日が承諾した日付より6ヶ月以上たった場合は、再度、承諾を得て下さい。

承諾した日付をご記入下さい。

年　　月　　日

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〒305-0074 茨城県つくば市高野台3－1－1
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研究推進部　企画課

(理研記入)
(受付日　　　年　　月　　日)
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(User No.　　　　　　　　)

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この同意書は必ず2部作成し、2部ともBRCに送付して下さい。
センター長押印後、1部お返しいたします。

091020
細胞
(書式-0003)

RIKEN BRC　　Cell Bank

提供を受ける細胞材料名をご記入下さい。
下記の「4」の提供制限が同じものは、複数記入できます。

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(理研BRC細胞材料開発室所有記号No.
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このリソースを用いる研究課題名をご記入下さい。
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4. 利用者は、本件リソースの利用に当たり、…理研BRCカタログ及びホームページに掲載されている、寄託者が指定した次の…条件を遵守する。

1/3

091020
細胞
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締結年月日：西暦　　年　　月　　日

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機関名：

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所在地：〒

センター長：　小幡　裕一　　印

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研究責任者：　　　印

機関長：　　　印

公印を押印下さい。大学の場合は学部長、研究所の場合は所長を想定いたしております。また、既に知的所有権に関する管理責任者が任命されている機関では、管理責任者の署名もしくは捺印をお願いします。

（理研記入）
（受付日　　年　　月　　日）
（受付番号　　　　　　）

3/3

2. オンライン入力による提供依頼

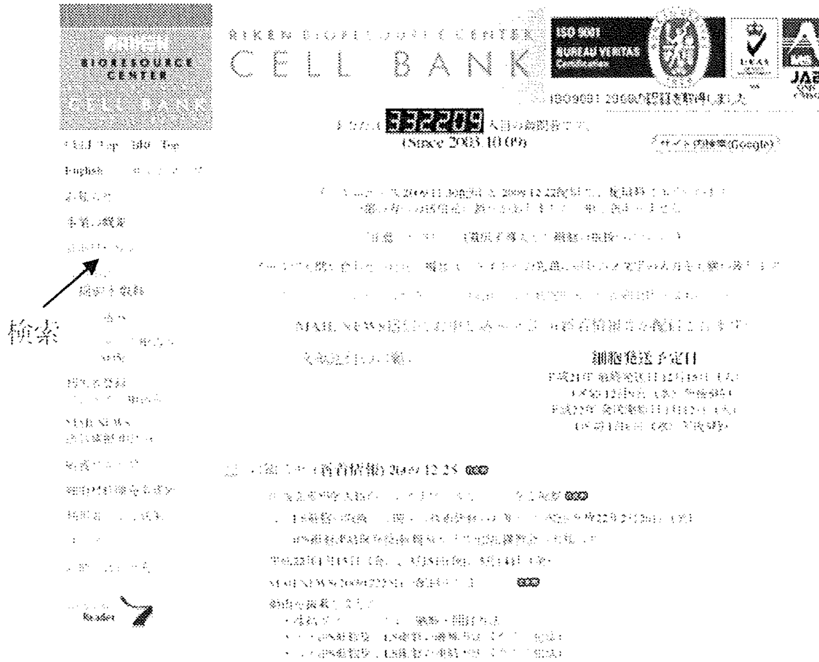
一般細胞（RCB）については、オンラインによる書類の作成が可能です。カタログの情報解析室のページおよび下記のホームページをご参照下さい。

http://www.brc.riken.jp/lab/cell/rcb/houto_online.shtml

補足:ホームページでの検索方法

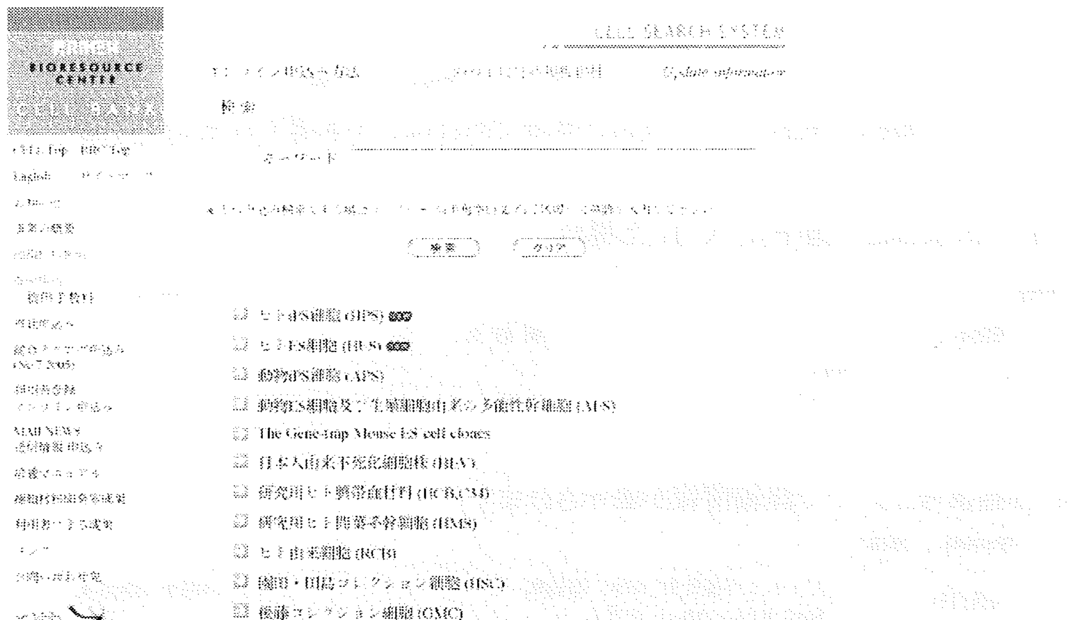
1. ホームページによる検索

http://www.brc.riken.jp/lab/cell/



2. 検索方法

リソースを検索する場合は、左のメニューの「細胞材料検索」をクリックして下さい。



すべての細胞材料が検索対象です。

3. キーワードを入力

(1) キーワードをご入力下さい。

例:「iPS」と入力した場合

Items 6 Search

細胞番号	細胞名
APS0001	iPS-MEF-Ng-20D-17
APS0002	iPS-MEF-Ng-178B-5
APS0003	iPS-MEF-Fb/Ng-440A-3
APS0004	iPS-MEF-Ng-492B-4
HPS0001	201B7
HPS0002	253G1

(2) さらに条件を絞り込む場合。

例:「iPS　human」

Items 2 Search

細胞番号	細胞名
HPS0001	201B7
HPS0002	253G1

TOP

Search キーワード iPS human

検索　クリア

＊　初めから、スペース(半角)で区切っての検索も可能です。

＊　各細胞の特性(日)に含まれる単語であれば、日本語での検索も可能です。

例:「iPS human 4 因子」と入力した場合

Items 1 Search

細胞番号	細胞名
HPS0001	201B7

(3) 細胞番号クリックで詳細情報が表示されます。

HPS0001 : 201B7

特性(日)	ヒト人工多能性幹（iPS）細胞株。レトロウイルスベクターにより4因子（Oct3/4, Sox2, Klf4, c-Myc）を導入。
動物種	human

II.　研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
小幡裕一、中村幸夫	組織のバンキングとディストリビューション	町野　朔	バイオバンク構想の法的・倫理的検討	上智大学出版	東京	2009	141-151
中村幸夫	幹細胞バンクの活用		幹細胞の分化誘導と応用	株式会社NTS	東京	2009	144-155

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Capes-Davis, A., Theodosopoulos, G., Atkin, I., Dreexler, H.G., Kohara, A., MacLeod, R.A.F., Master, J.R., Nakamura, Y., Reid, Y.A., Reddel, R.R., and Freshney, R.I.	Check your cultures! A list of cross-contaminated or misidentified cell lines.	*Int. J. Cancer*	127	1-8	2010
Yamazaki, Y., Akashi, R., Banno, Y., Endo, T., Ezura, H., Fukami-Kobayashi, K., Inaba, K., Isa, T., Kamei, K., Kasai, F., Kobayashi, M., Kurata, N., Kusaba, M., Matsuzawa, T., Mitani, S., Nakamura, T., Nakamura, Y., Nakatsuji, N., Naruse, K., Niki, H., Nitasaka, E., Obata, Y., Okamoto, H., Okuma, M., Sato, K., Serikawa, T., Shiroishi, T., Sugawara, H., Urushibara, H., Yamamoto, M., Yaoita, Y., Yoshiki, A., and Kohara, Y.	NBRP database: databases of biological resources in Japan.	*Nucl. Acids Res.*	38	D26-D32	2010

Nakamura, Y.	Induced pluripotent stem (iPS) cells offer a powerful new tool for the life sciences.	*J. Stem Cells Regen. Med.*	6	1-8	2010
Nakamura, Y.	Bio-resource of human and animal-derived cell materials.	*Exp. Anim.*	59	1-7	2010
Ishigaki, T., Sudo, K., Hiroyama, T., Miharada, K., Ninomiya, H., Chiba, S., Nagasawa, T., and Nakamura, Y.	Human hematopoietic stem cells can survive *in vitro* for several months.	*Advances in Hematology*	2009	ID936761	2009
Tamagawa, T., Ishiwata, I., Sato, K., and Nakamura, Y.	Induced *in vitro* differentiation of pancreatic-like cells from human amnion-derived fibroblast-like cells.	*Hum. Cell*	22	55-63	2009
Danjoh, I., Sone, H., Sekiyama, S., Mizukoshi, K., Noda, N., Iimura, E., Nagayoshi, M., Saijo, K., Hiroyama, T., and Nakamura, Y.	Is parainfluenza virus a threatening virus for human cancer cell lines?	*Hum. Cell*	22	81-84	2009
Nakamura, Y.	*In vitro* production of transfusable red blood cells.	*ISBT Science Series*	4	383-389	2009

III. 研究成果の刊行物・別刷

uicc
global cancer control

IJC
International Journal of Cancer

Check your cultures! A list of cross-contaminated or misidentified cell lines

Amanda Capes-Davis[1], George Theodosopoulos[1], Isobel Atkin[2], Hans G. Drexler[3], Arihiro Kohara[4], Roderick A.F. MacLeod[3], John R. Masters[5], Yukio Nakamura[6], Yvonne A. Reid[7], Roger R. Reddel[1] and R. Ian Freshney[8]

[1] CellBank Australia - Children's Medical Research Institute, Westmead, NSW, Australia
[2] European Collection of Cell Cultures (ECACC) - Health Protection Agency, Porton Down, Salisbury, Wiltshire, United Kingdom
[3] DSMZ - German Collection of Microorganisms and Cell Cultures, Braunschweig, Germany
[4] JCRB - Japanese Collection of Research Bioresources, Osaka, Japan
[5] Institute of Urology, University College London, London, United Kingdom
[6] RIKEN - BioResource Center Cell Engineering Division, Tsukuba, Japan
[7] ATCC - American Type Culture Collections, Manassas, VA
[8] Centre for Oncology and Applied Pharmacology, Glasgow University, Glasgow, United Kingdom

Mini Review

Continuous cell lines consist of cultured cells derived from a specific donor and tissue of origin that have acquired the ability to proliferate indefinitely. These cell lines are well-recognized models for the study of health and disease, particularly for cancer. However, there are cautions to be aware of when using continuous cell lines, including the possibility of contamination, in which a foreign cell line or microorganism is introduced without the handler's knowledge. Cross-contamination, in which the contaminant is another cell line, was first recognized in the 1950s but, disturbingly, remains a serious issue today. Many cell lines become cross-contaminated early, so that subsequent experimental work has been performed only on the contaminant, masquerading under a different name. What can be done in response—how can a researcher know if their own cell lines are cross-contaminated? Two practical responses are suggested here. First, it is important to check the literature, looking for previous work on cross-contamination. Some reports may be difficult to find and to make these more accessible, we have compiled a list of known cross-contaminated cell lines. The list currently contains 360 cell lines, drawn from 68 references. Most contaminants arise within the same species, with HeLa still the most frequently encountered (29%, 106/360) among human cell lines, but interspecies contaminants account for a small but substantial minority of cases (9%, 33/360). Second, even if there are no previous publications on cross-contamination for that cell line, it is essential to check the sample itself by performing authentication testing.

Key words: authentication, cell culture, cell lines, cross-contamination, DNA profiling, misidentification
Additional Supporting Information may be found in the online version of this article.

Novelty and Impact: This manuscript reviews the literature relating to cross-contamination of cell lines. Its novelty comes from the inclusion of a list of known cross-contaminated cell lines (over 300 lines named), allowing researchers to check their own cell lines with reference to the article. Recent developments in this field, including methods of authentication testing, are also discussed.

Grant sponsor: National Health and Medical Research Council of Australia
DOI: 10.1002/ijc.25242
History: Received 24 Nov 2009; Accepted 18 Jan 2010; Online 8 Feb 2010

Correspondence to: Amanda Capes-Davis, CellBank Australia, Children's Medical Research Institute, Locked Bag 23, Wentworthville, NSW 2145, Australia, Fax: +61 2 9687 2120, E-mail: acapdav@gmail.com

Int. J. Cancer: **127**, 1–8 (2010) © 2010 UICC

Cell Lines as Model Systems

Continuous cell lines represent a readily accessible and easily studied resource for research into health and disease. These cell lines have acquired the ability to proliferate indefinitely if grown in the appropriate culture conditions; usually this is a rare event, since the majority of cells even in tumor tissue will cease proliferation after a limited number of cell divisions.[1] However, once established, a continuous cell line can be repeatedly passaged, reliably recovers from cryopreservation and retains many of the properties of its cell type or tissue of origin.[2,3] These advantages make continuous cell lines effective, and widely used, model systems for normal cellular processes and for a variety of disease states.

Cell lines are particularly attractive models for studying malignant disease. The genetic changes in tumor-derived cell lines closely resemble those of the tumors of origin.[4] Moreover, the genetic changes required to establish continuous cell lines from normal cells recapitulate many of the genetic changes occurring in cancer.[5,6] These genetic changes are required to overcome replicative senescence, in which normal cells continue to be metabolically active but are restricted from further division.[1] Cells able to overcome senescence continue

proliferating until their telomeres become so short that the chromosomes undergo fusion-breakage-bridge cycles and the ensuing genomic instability results in culture crisis. Occasionally (at a rate of ~1 in 10^7 cells), an immortalized cell will emerge from crisis and begin to divide again, yielding a continuous cell line.[1] The changes seen throughout this process have many parallels within cancer development, both for malignancy in general and when considering specific tumor types.[7,8]

Despite these advantages, numerous cautions have emerged from the literature regarding appropriate use of cell lines as model systems.[9,10] Even where cultures have been transformed through the introduction of specific genes, cell lines that have passed through replicative senescence and crisis are aneuploid, heteroploid and genotypically and phenotypically unstable, resulting in considerable heterogeneity within the culture.[10] This instability will cause changes in the characteristics of the cell line but a further consequence may result: alterations in a cell line can be accepted by the user as intrinsic to that culture when there is actually extrinsic contamination present.

Cell Line Cross-contamination and Misidentification

Cell lines become contaminated when a foreign cell line or microorganism is introduced without the handler's knowledge. Although we do not wish to minimize the problem of microbial contamination, we will focus on cell line cross-contamination in this article. Cross-contamination may arise due to several causes, including poor technique (spread *via* aerosols or accidental contact), use of unplugged pipets, sharing media and reagents among cell lines and use of mitotically inactivated feeder layers or conditioned medium, which may carry contaminating cells if not properly eliminated, for example, by freeze-thaw and filtration.[11] In addition, a cell line can be replaced by another as a result of misidentification by confusing cultures during handling, mislabeling or poor freezer inventory control. Simple errors during labeling of culture flasks, truncation of the cell line name or typographic errors in a published manuscript, can result in significant confusion for years after the event when another researcher attempts to use the same cell line for ongoing experimental work.[12]

Cross-contamination may occur "early," in which case the original cell line has probably never existed independently, or "late," where the tested sample has been overgrown but other stocks of the original may still exist.[13] Unfortunately, cell lines generally become cross-contaminated early, while still within the originating laboratory.[14] This is not surprising: cultures can remain in crisis for a prolonged period of time before emergence of an immortalized population and this is a time when a single cell, if introduced from a separate cell line, would rapidly take over the culture.

There are now a number of studies pointing out the severity of this problem and the need to take urgent action to minimize cross-contamination and its consequences.[9,15–17] Ten years ago, the German Collection of Microorganisms and Cell Cultures (DSMZ) published data from its identification testing of cancer cell lines submitted by various laboratories for deposit at the cell bank.[14] They found that 18% of 252 submitted cell lines were cross-contaminated with more than half of cases arising within only 6 laboratories. Subsequent work by the DSMZ, extending the number of cell lines tested (Fig. 1), shows that of 598 leukemia–lymphoma cell lines (the group provided with the most complete genetic data), 187 (31%) were contaminated with Mycoplasma and/or a second cell line with 38 (6%) of cell lines contaminated with both. These data suggest that poor practice within some laboratories results in contamination of multiple cell lines with multiple contaminants, which can then be disseminated more widely if these cultures are used by others.

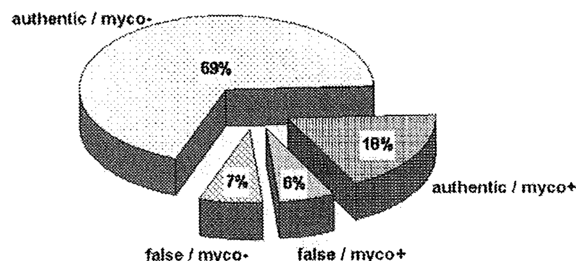


Figure 1. Rates of contamination for leukemia–lymphoma cell lines. Percentages of cross-contaminated and Mycoplasma-contaminated cell lines from a dataset of 598 leukemia and lymphoma cell lines analyzed by the German cell line bank DSMZ. "False/authentic" refers to the presence or absence of cross-contamination; "myco+/myco−" refers to the presence or absence of Mycoplasma contamination. Cell lines fall into the following categories: authentic/myco− (n = 411, 69%); authentic/myco+ (n = 108, 18%); false/myco− (n = 41, 7%) and false/myco+ (n = 38, 6%). (Courtesy of Hans Drexler, DSMZ.)

Other studies have pointed out that testing of cell lines is often infrequent, resulting in the failure to detect contaminated samples. John Ryan of Corning Life Sciences conducted surveys of seminar attendees in 1990, asking about Mycoplasma contamination; 50% were not currently performing testing and only 18% said they tested their cultures regularly. Almost 1 in 4 respondents (23%) had experienced Mycoplasma contamination, but with such a low level of testing, it is likely that the real figure was much higher.[18] Other data on cross-contamination were published in 2004 by researchers at the University of California, Berkeley, where Walter Nelson-Rees worked on this problem in the 1970s, focusing on the HeLa cell line.[19] Of 483 respondents to a questionnaire on cell line usage, 35% were using cell lines obtained from another laboratory rather than a cell line repository, but almost half of all respondents performed no testing for cross-contamination.[20]

A practical example of the consequences of cell line contamination can be found in a recent study published by Berglind *et al.*[21] The authors analyzed data within the UMD_p53 (2007) database, which includes information on the p53 status of 1,211 cell lines. Discrepancies were found in p53 status for 23% (88/384) of cell lines where data have been published by 2

independent laboratories. It is likely that many of these discrepancies arose due to work with cross-contaminated samples; the authors noted that many groups rely on previously published reports of a cell line's p53 status,[21] resulting in further confusion when interpreting results from these cell lines.

Cell banks have the expertise to detect such cross-contamination, and have been proactive in publishing reports of cross-contaminated cell lines,[22,23] in publishing test results online[24] and in developing new detection methods.[25–27] Unfortunately, however, cell banks have also reported reluctance from many researchers to deposit cell lines for distribution.[28] Such repositories specialize in the detection of cross-contamination and it is unlikely that most laboratories have comparable resources in this regard. In addition, many researchers obtain cell lines from one another, rather than approaching the originator or purchasing the cell line from a cell bank performing quality control testing. This may be faster or cheaper than obtaining cultures from a reputable source but the practice makes contamination more prevalent and harder to detect.

Practical Responses

Having defined the problems, it is time to focus on what can be done. Several cancer-related journals, including the International Journal of Cancer, have recently responded to these issues by changing their policies to require evidence of authentication with all submitted manuscripts using continuous cell lines.[29,30] Their response underscores the need for laboratories to come to grips with cell line cross-contamination and misidentification. Every researcher involved in cell culture will have cell lines currently in culture, stored in liquid nitrogen or may be commencing work on a new cell line. Put practically, how can you know if your cell lines are cross-contaminated?

There are 2 important answers to this question:

1. Check the literature, for example, by searching the PubMed database using the cell line name and "cross-contamination."
2. Check your cultured cells. Unless a cell line has come directly from a repository or other laboratory performing identification testing, it should be tested on arrival, and all cultures should be periodically tested while in use, before cryopreservation and when thawed from liquid nitrogen.[31] A variety of methods are available for authentication; for human cell lines, short tandem repeat (STR) profiling is the current international reference standard and is recommended as an easy and economical way to confirm cell line identity by comparison to donor tissue or to other samples of the cell line held by laboratories worldwide.[26]

Checking the Literature: A List of Cross-Contaminated Cell Lines

A 2004 survey of abstracts within the PubMed database would suggest that inappropriate usage of cross-contaminated cell lines is increasing,[20] despite many years of publication on this issue. It is possible that many researchers simply cannot find existing references to cross-contamination so, to make this already published work more accessible, we have surveyed the literature and other online resources for references to cell line contamination. The resulting list of cross-contaminated cell lines is included as Electronic Supporting Information.

To generate this list, the authors examined the PubMed database, references within other articles relating to this topic and the websites of 5 cell banks: the American Type Culture Collection (ATCC), DSMZ, European Collection of Cell Cultures (ECACC), Japanese Collection of Research Bioresources and the RIKEN Bioresource Center Cell Bank. A Wikipedia list of contaminated cell lines was also accessed (http://en.wikipedia.org/wiki/List_of_contaminated_cell_lines). Cross-contaminated cell lines are listed by name along with their species and cell type (both claimed and actual), the name of the contaminating cell line where identified, the reference in which this was reported and the PubMed ID number where available. Notes are also included for some cell lines. The list is made available in Excel spreadsheet or PDF format for easy accessibility.

The cell lines listed within this database are divided into 2 tables. Supporting Information Table 1 contains those cell lines where cross-contamination occurred as an early event, and thus where there is no original material remaining. Supporting Information Table 2 contains those cell lines where it is thought cross-contamination occurred as a late event and where original stocks may still exist. A full list of references is also given.

The current list of cross-contaminated cell lines (version 6.4) contains 360 cell lines, 346 in Supporting Information Table 1 and 14 in Supporting Information Table 2, drawn from 68 references. Cell lines affected are primarily human, although cultures from at least 8 other species are included, and come from a wide spectrum of tissue types. The cell or tumor type is given within the list where known; extensive work has been done by some cell banks and laboratories in this area to characterize the actual cell type or tumor type.[22,32] In some cases, this work has shown that a cell line carries the correct name but its cell or tumor type has been incorrectly identified, for example, the cell line RPMI-6666 was initially thought to have come from Hodgkin lymphoma but is now known to be an EBV-positive B-lymphoblastoid cell line.[22]

Common features for cross-contaminating cell lines within the current list are summarized in Table 1. It can be seen that most cross-contamination events have arisen from within the same species but a substantial minority (9%, 33/360) involved cross-contamination from a second species. For the intraspecies contaminants, all of those detected were human but it is likely that this relates to the difficulty of detecting intraspecies contaminants for nonhuman species. The commonest contaminant remains the HeLa cell line

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Table 1. Cross-contaminating cell lines

Type of contaminant	Number of cell lines affected
Intraspecies	
Human	324
Nonhuman	0
Interspecies	33
Correct name—incorrect cell type (misidentified)[1]	3
Total	360
Contaminating cell line—12 most frequent	**Number of cell lines affected**
HeLa (human cervical adenocarcinoma)	106
T-24 (human bladder carcinoma)	18
HT-29 (human colon carcinoma)	12
CCRF-CEM (human acute lymphoblastic leukemia)	9
K-562 (human chronic myeloid leukemia)	9
U-937 (human lymphoma)	8
OCI/AML2 (human acute myeloid leukemia)	8
Hcu-10 (human esophageal carcinoma)[2]	7
M14 (human melanoma)	7
HL-60 (human acute myeloid leukemia)	6
PC3 (human prostate carcinoma)	6
SW-480, SW620 (human colon carcinoma)[3]	6

[1]For additional misidentified cell lines see Drexler *et al.*[22] [2]Hcu-10 carries the same genetic identity as Hcu-18, Hcu-22, Hcu-27, Hcu-33, Hcu-37 and Hcu-39; it is unclear which is the correct identity (see Electronic Supporting Information for reference). [3]SW480 and SW620 come from the same donor and therefore carry the same genetic identity (see Electronic Supporting Information for reference).

(29%, 106/360), followed by T-24 (5%, 18/360) and HT-29 (3%, 12/360).

It is important for such a list to be continually updated and feedback is welcome for this purpose. An earlier version of the database was released online by ECACC[31]; 6 cell banks have now agreed to make the database available online and to update this information where necessary. Current website addresses for access to the list of cross-contaminated cell lines are given in Table 2. In future, it is envisaged that the current list of misidentified cell lines will be included in a new initiative improving access to authentication data. The Standard Development Organization at the ATCC is in the process of producing an international standard for human cell line identification based on STR profiling (ATCC SDO Workgroup ASN-0002, manuscript submitted). Strict criteria for STR profiles derived from cancer cell lines are being developed. One consequence of this initiative is that funding is being sought for a quality controlled and curated cell line database with free access into which the database described here will be incorporated.

Table 2. Websites for ongoing access to the list of cross-contaminated cell lines

Cell bank	Website address
ATCC	http://www.atcc.org/
CellBank Australia	http://www.cellbankaustralia.com/
DSMZ	http://www.dsmz.de/
ECACC	http://www.hpacultures.org.uk/collections/ecacc.jsp
JCRB	http://cellbank.nibio.go.jp/
RIKEN Bioresource Center Cell Bank	http://www.brc.riken.go.jp/lab/cell/english/guide.shtml

Checking Your Cultures: Authentication of Cell Lines

Even if a search of the literature shows no indication that a cell line is contaminated, it is still essential to test the sample that you are working with. Authentication testing should be considered in a positive light, as an essential part of good cell culture practice[33] and as an assurance for researchers, funding bodies and journals that the cell line used is a valid experimental model.[17]

There are a number of methods for testing cell line identity. When the issue of cross-contamination was first identified, HeLa contaminants were detected through a combination of isoenzyme and chromosomal analysis.[19,34] Both techniques continue to be used but there are also many newer molecular approaches. Commonly used authentication methods are summarized in Table 3; what factors should be considered when choosing between these methods?

The expertise of the laboratory holding the cell line is an important factor. For example, laboratories with experience in cytogenetics would have the skills to identify species through karyotype analysis and cell lines through the presence or absence of appropriate markers.[35] Although this is an older approach, it still allows clear identification of cell lines, and many cell banks have published karyotypic information on their cell lines to allow comparison to well-characterized stocks. It should be noted that tumor-derived cell lines can be surprisingly difficult to harvest for cytogenetic analysis[35] and are typically heteroploid making interpretation difficult: the experience of the operator is important for success.

The species of cell lines held within the laboratory is also important. Although some authentication methods can be used on more than 1 species, molecular methods such as STR profiling are only successful for a single species; other species will simply fail to amplify.[26] This may not be an issue for laboratories working only with human samples but clearly is a significant factor for groups working with rodent cell lines. In this regard, multilocus DNA fingerprint analysis has a clear advantage, since probes are able to hybridize to a wide variety of species.[25] Unfortunately, although successful within a single laboratory, it can be challenging to compare DNA fingerprints across several experimental runs, and it is difficult to exchange data among laboratories or for cell

Table 3. Commonly used methods for authenticating cell lines

Name	Description	Purpose	References
Chromosomal analysis/karyotyping	Involves preparation of a metaphase spread with chromosome banding and painting to identify chromosome number and markers	Separates species, plus individual cell lines if detailed analysis performed	Ref. 35
Isoenzyme analysis	Biochemical method separating isoenzymes by electrophoresis; isoenzyme mobility may vary within or across species. Kits available include the Authentikit gel electrophoresis system	Separates species, sometimes individuals	Refs. 36,37
Multilocus DNA fingerprint analysis	Molecular method detecting variation in length within minisatellite DNA containing variable numbers of tandem repeat sequences. Analysis is by Southern blot hybridization using probes 33.6 and 33.15, M13 phage DNA, or oligonucleotide sequence	Separates individual cell lines across multiple species	Refs. 25,38
Short tandem repeat (STR) profiling	Molecular method detecting variation in length within microsatellite DNA containing variable numbers of short tandem repeat sequences. Analysis is by PCR with comparison to set size standards; usually available in a kit format allowing amplification of up to 16 loci	Separates individual cell lines within a single species	Refs. 26,39
Polymerase chain reaction (PCR) fragment analysis	Molecular method involving amplification of specific genes or gene families, aiming to detect variations in exon/intron sequence, transcript splicing, or the presence of pseudogenes. Genes examined include the aldolase gene family and the beta-globin gene	Separates species only	Refs. 40,41
Sequencing of "DNA barcode" regions	Involves sequencing of a DNA fragment from the mitochondrial gene cytochrome *c* oxidase subunit I, with comparison to sequence obtained from online databases. This "DNA barcode" has been shown in practice to distinguish a broad range of animal species	Separates species only	Refs. 27,42

banks to publish such fingerprints online. It is advisable to always compare the test sample to a known sample within the same experiment, ideally using DNA from the blood or tissue of the original donor.

The obvious advantage of STR profiling lies in the use of control samples to generate a numerical code for each sample, which precisely identifies that cell line and which can be readily shared and published online. It is primarily for this reason that STR profiling is recommended as an international reference standard for human cell lines[26] and accepted within the legal system for human identity testing.[39] STR profiling is based on the presence of STRs within the human genome that exist at variable lengths throughout the population. Each of the repeat regions to be analyzed (usually tetra or pentanucleotide repeats in noncoding sequence) is amplified by PCR using primers carrying fluorescent tags and electrophoresed in a sequencing gel; the precise length of each allele is determined and compared with size standards and controls. This allows identification software to assign a number to each allele at that locus (see, *e.g.*, Fig. 2). The combination of multiple loci—classically 13, as used in the FBI Laboratory's Combined DNA Index System (CODIS)—gives sufficient data to uniquely identify that individual.

STR profiles for individual cell lines and panels have now been reported by many laboratories (*e.g.*, Ref. 44) and are published online by several cell banks. However, there are some cautions to be aware of when using this approach. It is accepted within the forensic field that tumor samples are not as genetically stable as other tissue sources for STR profiling, because of loss of heterozygosity and microsatellite instability.[45,46] This is even more evident in tumor-derived cell lines, where evolution or genetic drift continues to occur with passage.[47] When searching an online database of STR profiles from cell lines, the user needs to look for close matches and not just identical matches; most studies would agree that 80% similarity is an appropriate threshold for declaring a match when comparing cell line profiles.[26,44] There may also be a significant start-up cost if testing in-house; in addition to an STR kit, access to methods for DNA extraction, precise quantitation, fragment analysis and software for STR profile identification is required.

The fact that STR profiling is only suitable for distinguishing cell lines of a single species has led to the need to re-examine authentication of nonhuman cell lines. Laboratory rodent samples will always be difficult to identify precisely due to inbreeding; laboratories working with rat or mouse cultures may wish to examine strain identity rather than authentication of individual cell lines, particularly if they have expertise in single nucleotide polymorphism (SNP) or single sequence length polymorphism (SSLP) analysis,

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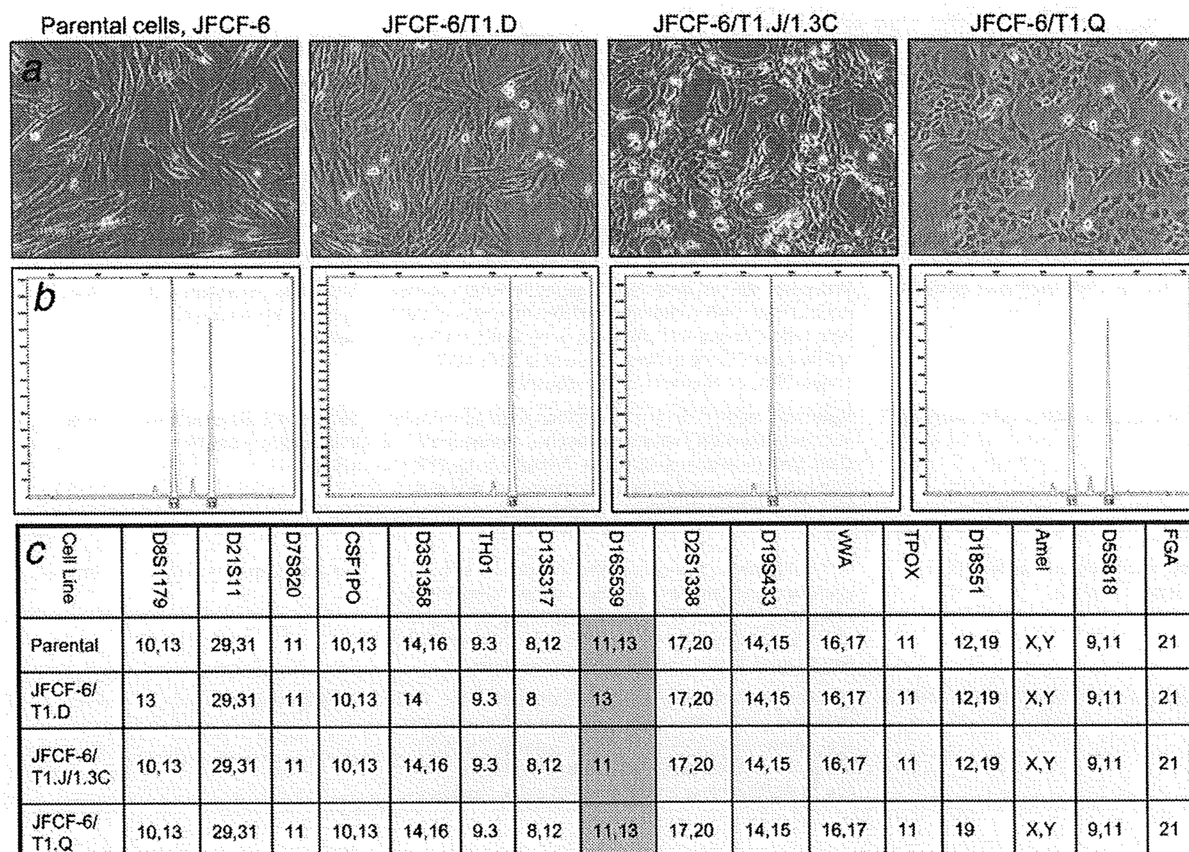

Cell Line	D8S1179	D21S11	D7S820	CSF1PO	D3S1358	TH01	D13S317	D16S539	D2S1338	D19S433	vWA	TPOX	D18S51	Amel	D5S818	FGA
Parental	10,13	29,31	11	10,13	14,16	9.3	8,12	11,13	17,20	14,15	16,17	11	12,19	X,Y	9,11	21
JFCF-6/ T1.D	13	29,31	11	10,13	14	9.3	8	13	17,20	14,15	16,17	11	12,19	X,Y	9,11	21
JFCF-6/ T1.J/1.3C	10,13	29,31	11	10,13	14,16	9.3	8,12	11	17,20	14,15	16,17	11	12,19	X,Y	9,11	21
JFCF-6/ T1.Q	10,13	29,31	11	10,13	14,16	9.3	8,12	11,13	17,20	14,15	16,17	11	19	X,Y	9,11	21

Figure 2. Example of STR profile generation and interpretation. An example of STR profiling is given for the JFCF-6 cell fibroblast strain and 3 of its immortalized derivatives, JFCF-6/T1.D, JFCF-6/T1.J/1.3C and JFCF-6/T1.Q.[43] Derivatives were established after transfection with SV40 early region DNA and were handled by CellBank Australia through its Culture and Return service. DNA from each culture was amplified using the AmpFlSTR Identifiler PCR Amplification Kit (Applied Biosystems, Mulgrave, Australia), which includes primers for 16 STR loci. Amplified sequence was analyzed using an ABI PRISM 3100 Genetic Analyzer and data files were assessed using GeneMapper ID software (Applied Biosystems). (*a*) Photographs taken of each culture, comparing parental cells to the morphology of each derived cell line (scale bar = 100 μm). Each derivative has a markedly different morphology, showing the need for authentication testing to confirm that derivatives correspond to the parental strain. (*b*) Examples of STR peak amplification for the D16S539 locus of each culture. Amplification varies at this locus due to genetic drift during establishment of the 3 JFCF-6–derived cell lines. The peaks shown correspond to specific allele sizes known to exist at this locus and confirmed using size standards and controls supplied with the kit (data not shown). (*c*). STR profiles for JFCF-6 and derived cell lines; the locus shown in B, D16S539, is highlighted in grey. Despite the differences seen due to genetic drift, the profiles for derived lines closely match the parental cell strain and all of these cultures are correctly identified.

which can be used for strain identification.[48,49] SNP analysis can also be used to identify individual samples[50] and has been used for cell line authentication,[51] making it a method of great promise for application to human and nonhuman samples alike. Laboratories working on specific cell types may be able to use expressed markers for identification, as 1 laboratory has done recently, publishing a technique for identification of hybridomas based on sequencing of light-chain variable regions.[52]

A simple method has recently emerged to help detect interspecies contamination. The term DNA barcoding here refers to amplifying a specific 648 bp fragment of the mitochondrial gene, cytochrome *C* oxidase subunit I (COI), using primers developed by Folmer *et al.*[53] Sequence divergences within this fragment allow species discrimination across almost all animal phyla.[42] Although debate is ongoing as to whether DNA barcoding is sufficient for assignment of species in taxonomic terms,[54] it is clear that the technique can readily identify the species of an unknown specimen if compared with previously sequenced reference material in online databases.[55] DNA barcoding has been tested for species identification of cell lines[27] and its use would reduce the incidence of interspecies cell line

contamination, found here to cause almost 1 in 10 of all published cross-contamination events.

Whatever the authentication method used, it should be clearly recorded within the researcher's experimental notes, and the result should be linked if possible to the laboratory's liquid nitrogen records, so that quality control for frozen vials is clearly evident. When publishing experimental work, the Material and Methods section should include the correct and full name of the cell line used, its origin (with appropriate references), the source of the cultures used and details of authentication testing.

Conclusions

Cell line contamination is a serious issue that detracts from the use of cell lines as model systems to help us understand a broad range of diseases, including cancer. Responding practically by checking each cell line before it is used, searching for previous references and authenticating the sample itself is worthwhile and will reduce the risk and subsequent consequences of contamination long-term.

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NBRP databases: databases of biological resources in Japan

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ABSTRACT

The National BioResource Project (NBRP) is a Japanese project that aims to establish a system for collecting, preserving and providing bio-resources for use as experimental materials for life science research. It is promoted by 27 core resource facilities, each concerned with a particular group of organisms, and by one information center. The NBRP database is a product of this project. Thirty databases and an integrated database-retrieval system (BioResource World: BRW) have been created and made available through the NBRP home page (http://www.nbrp.jp). The 30 independent databases have individual features which directly reflect the data maintained by each resource facility. The BRW is designed for users who need to search across several resources without moving from one database to another. BRW provides access to a collection of 4.5-million records on bioresources including wild species, inbred lines, mutants, genetically engineered lines, DNA clones and so on. BRW supports summary browsing, keyword searching, and searching by DNA sequences or gene ontology. The results of searches provide links to online requests for distribution of research materials. A circulation system allows users to submit details of papers published on research conducted using NBRP resources.

INTRODUCTION

Japanese bioresources for life science research have an 80 year history. Although some unique and precious collections of resources have been accumulated during this time, some of these have recently became dispersed and lost as a result of the increasing age of their providers or through shortages of funds, so that systems for providing useful collections of resources became inadequate. To improve this situation, it was necessary to establish a sustainable environment in which researchers could readily obtain bioresources, so the National BioResource Project (NBRP) began in 2002. The species included in the project were selected on the basis that they were indigenous to Japan or that they were model organisms currently studied or expected to be studied in the future by large numbers of researchers.

A major feature of this project is that it promotes the centralization of resources and information to ensure continuity. Resources are organized by species or groups of organisms, and a system of interaction between the resource and the information center [which belongs to the National Institute of Genetics (NIG)] was created to centralize the information. All the information in the databases is publicly available and several enhancements

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