Terms of Reference

What Do We Mean by Cell Line Misidentification?

A cell line is misidentified if its DNA profile is no longer consistent with the donor from whom it was first established. Such a cell line can be described as a misidentified cell line, or as a false or imposter cell line. Investigators who are unaware that they are working with a false cell line may use it in their work, without realising that it comes from an entirely different cell type or tissue – perhaps even a different species – and is likely to be unfit for their application. This lack of awareness leads to unreliable research findings, and the use of those unreliable findings by other scientists in turn.

Although there are many causes of false cell lines, including mislabelling of culture samples, the problem is often caused by cross-contamination (see the Definitions later in this document). Many cell lines have been cross-contaminated during establishment and so all subsequent work based on the false cell line has used the contaminant rather than the correct species, tissue or cell type that was originally present in that culture. Once cross-contaminated, cell lines are often handed from laboratory to laboratory without anyone being aware that their stocks may be unfit for use. This practice can only lead to confusing results and represents a waste of precious resources.

Why Do We Focus on Cell Line Authentication?

Authentication testing is an effective way to combat the use of false cell lines. Authentication testing aims to compare a test sample to other reference samples from that donor, or to a database of reference samples if donor material is not available, to see whether samples correspond. The test method should distinguish between different species and different individuals within that species, although this will depend on the technology available to the field of authentication testing. When multiple cell lines have been established from a single individual, identification rests on additional test methods and characteristics such as tissue-specific markers, phenotype and morphology. While all such testing falls within the realm of authentication, the latter methods are unreliable as identity tests and therefore these aspects of authentication are outside the scope of this document.

In 2011, the American Type Culture Collections Standard Development Organization (ATCC SDO) published a standard on authentication testing of human cell lines (ANSI/ATCC ASN-0002-2011). A new group, the International Cell Line Authentication Committee (ICLAC), was formed after publication of the standard to provide guidance and an ongoing focus for improvement in this area.

ICLAC aims to make the use of false cell lines more visible and to promote awareness and authentication testing as effective ways to combat the problem.

Goal 1: Make Cell Line Misidentification More Visible

A number of laboratories and cell line repositories have uncovered false cell lines, in publications dating from the 1960s. More information will come from public databases such as the NCBI cell line database, currently in preparation as part of the standard. These online, interactive databases give cell banks and laboratories an effective way to compare samples and share authentication test results. But it is important that the older reports are not lost and that any incorrect or inaccurate information added to the literature, or to online databases, should be addressed.

To make this information more visible and informative, ICLAC aims to:

1. Review reports of misidentified or cross-contaminated cell lines
2. Gather information to provide a written response, where needed, to the scientific community
3. Manage a master list of misidentified cell lines for the research community and for feedback to the NCBI cell line database

As a resource for the research community in this area, members of the group have previously developed a single list of cross-contaminated or misidentified cell lines. The list will be used as an initial template for this goal, with ongoing updates and online release of updated information. It can

then be used as a tool to help ensure that reports of cell line misidentification are recorded, made accessible to the research community, and any inaccuracies are corrected.

Goal 2: Promote Authentication Testing

The standard referred to above is an important resource for authenticating human cell lines. However, there is a need for education and resources to help laboratories apply the standard in their own situations.

How this is done will depend on the resources available to the group. Possibilities include:

- Provide advice to scientists planning a project or grant application, starting new work or initiating new cell lines
- Guidelines and protocols on application of the standard and recommended test measures
- Shared policies on difficult issues
- Shared data to provide more effective datasets for shared online databases
- Approaches to journals and funding bodies to encourage mandatory authentication testing, with assistance if needed to make such testing recommendations easier to make.

Goal 3: Harmonization of Guidelines and Standards

In addition to the standard referred to above, other standards and guidelines are relevant to authentication testing or – more broadly – to good cell culture practice.

Use of standards and guidelines may vary from country to country because of different regulatory frameworks. Use may also vary from one application to another, depending on the type of cell culture being performed. However, it is important to maintain consistency across all reference documents wherever possible, so that laboratories are not faced with conflicting requirements. ICLAC aims to assist in harmonization of relevant guidelines and standards by providing an independent forum for communication and discussion of such reference documents as they arise.

Ground Rules

ICLAC members have been invited to join the group based on expertise in cell line misidentification, authentication testing, or database applications. Members act in a voluntary capacity and their individual contributions and commitment to addressing the problem of cell line misidentification are respectfully acknowledged.

Contributions from members are subject to the policies of their individual institutions. All shared policies and sharing of data must be approved by the contributing organisation.

The committee meets every three months by teleconference. Correspondence and other business are carried out by email as far as possible, to allow members from different time zones to contribute.

A new finding of cell line misidentification can be reported by any member. New reports will be distributed to the members with an opportunity to give feedback and contribute further data where available. If members accept or endorse the initial report, the curator of the list of cross-contaminated or misidentified cell lines will add that entry to the list. If any member challenges the initial report, the cell line will be reviewed by the members and a decision made on its status based on available data. A lack of a response from a member will be taken as agreement to the cell line being added to the list.

A change in status for cell lines already entered on the list can be reported using a similar process. For example, if authentic stock is found, the cell line can be moved from Table 1 (no known authentic stock) to Table 2 (authentic stock known).

Duration and Terms of Reference

No duration has been set for the committee. To promote effective use of resources, the committee will review its purpose and goals on an annual basis via teleconference. The Terms of Reference can be modified by the group following teleconference discussion. All changes must be reviewed by the members via email before being adopted.

Definitions

Some words are used in many different ICLAC documents and resources. They include:

Authentication. The aim of authentication is to confirm or verify the identity of a cell line, ensuring that it is derived from the correct species and donor. Testing involves comparison of a test sample to other reference samples from that donor, or to a database of reference samples if donor material is not available, to see whether samples correspond. Ideally, the test method should distinguish between different species and different individuals within that species, although this will depend on the technology available to the field of authentication testing. Not all currently used test methods have the power of discrimination of STR profiling or SNP testing; therefore authentication may not in all cases lead to unambiguous identification of cells to a specific donor or donor tissue. Where unambiguous identification is not possible, species verification is used as the best alternative currently available.

Cross-contamination. The term contamination refers to introduction of foreign material into a cell culture. Cross-contamination occurs when that foreign material consists of cells from another culture. Cross-contamination initially results in a mixed culture, containing cells from the authentic culture and the contaminant. If the contaminant has a survival advantage – for example, if it proliferates more rapidly – it will overgrow and replace the authentic cells within the culture. A contaminant usually comes from a different donor or species and so can be detected by authentication testing.

Misidentification. A misidentified cell line no longer corresponds to the donor or species from which it was originally established. Misidentification may arise due to cross-contamination. It may also arise from a variety of errors, including mislabelling of samples. If it happens early – for example, during cell line establishment – there will be no authentic material retained, and the cell line will be considered to be a false cell line. If misidentification happens late – for example, after the cell line is established and distributed to other locations – then authentic material may still exist and only some stocks may be false.

Misidentification does not refer to problems with the technical procedure of authenticating cell lines. It also does not typically extend to other characteristics such as tissue type, cell type or disease state. If the tissue type, cell type or disease state of a cell line is incorrectly attributed, the cell line is considered to be misclassified.

Members

Information on what the ICLAC members do can be found in the Ground Rules section.

A full list of committee members and their affiliations can be found on the ICLAC website.

Partner Organizations

Organizations have provided support to ICLAC since inception in a number of ways, including administrative support; website resources; sourcing of cell line samples; and sample testing. Organizations have also enabled staff to contribute their time as ICLAC members. We wish to acknowledge all of the organizations who have supported the work of the committee in different ways.

A full list of partner organizations and funding sources can be found on the ICLAC website.