

Clinical Translation of Adult Stem Cell Lines (PDF Version)

The ISSCR (International Society for Stem Cell Research) states, “The level of regulation and oversight should be proportional to the degree of risk raised...and intended use (autologous versus allogeneic use, minimally versus highly manipulated cell products, use for homologous versus non-homologous functions).” (See <http://www.isscr.org/clinicaltrans/pdfs/ISSCRGLClinicalTrans.pdf> accessed April 10, 2009). The ICMS concurs with this position, and thus the focus of these guidelines is on autologous cell therapy in which the source of the A-ASC is functionally homologous with the therapeutic target. In addition, in order to balance patient safety with the availability of therapy, the ICMS has purposely narrowed its focus to cells which have been minimally culture expanded using techniques which mimic normal physiology.

For the purposes of these guidelines **minimal culture expansion** is defined by both period of incubation and number of culture passages of stem cells, in that the former may not exceed 60 days and the latter may not exceed 10 passages after colony formation).

It should be noted that at this time, that due to a lack of data regarding safe usage, the ICMS does not believe the following stem cell types are ready for clinical translation:

- Induced Pluripotent Cells (IPS)
- Embryonic or Cord Stem Cells
- Autologous Adult Stem Cells where genes have been manipulated

Translation of Stem Cells to Clinical Work:

The ICMS recognizes that pre-clinical trials and early clinical work should focus on safety. While clinical outcomes are important, since the use of stem cells are in early pre-clinical status for many disease applications, complications tracking is currently of paramount importance. Safety tracking can be broken into two basic components:

1. Transplant safety: The focus here is tumorigenesis, transplant site monitoring, and new disease monitoring. While these risks are believed to be minimal for therapy involving A-ASCs (as defined by ICMS), they are nonetheless inherent risks of A-ASC transplants.
2. Treatment specific risks: Every A-ASC transplant can pose specific risks based on transplant location, the disease being treated, and cell type. As an example, a cardiac treatment focused on implanting cells in the coronary artery would pose more inherent physical risks than a cosmetic transplant.

Clinical Safety Record:

ICMS has established a process to balance safety with the availability of treatment. This process involves clinical translation staging for cell lines. The cell line is first broken into one of two categories:

1. Established in Prior Human Testing: The cell line has passed the staging below in all categories. Once a cell line is established for one tissue type, it's known as "Clinical Grade" or CG
2. Unestablished in Prior Human Testing: The cell line has not passed the staging below in all categories.

The ICMS then breaks "Un-established in Prior Human Testing" cell lines into the following use categories for the purposes of clinical translation.

Clinical Staging for Cell Lines

Pre-Investigational Cell Line (PICL): No animal data is available. These cell lines should not be used in humans until animal data is available.

Early Investigational Cell Line (EICL): This is an un-established stem cell line being used in a new tissue where several animal models exist that show efficacy and safety, but no human data exists. An un-established cell line can be used in early stage human studies where 5-10 patients are treated and followed for a minimum of 6 months. The physician should be able to document subjective and objective outcome measures. Once these criteria are met and no significant complications have been reported, the cell line moves to the next grade. Note that before LICL patients can be treated, a minimum of 6 months follow-up is required at EICL.

Late Investigational Cell Line (LICL): This is an un-established stem cell line being used in a new tissue and is being tested in humans in larger numbers, typically 20-50 patients who are followed for a minimum of 6 months. The physician should be able to document subjective and objective outcome measures. Once these LICL criteria are met and no significant complications have been reported, the cell line moves to the next grade. To move onto treating ECCL patients, at least 20 of the LICL patients should be at the 6 month follow-up stage and have no complications.

Early Clinical Cell Line (ECCL): This is an un-established stem cell line being used in a new tissue and is being used for early stage clinical treatments in 50-200 patients that are followed for a minimum of 6 months. The physician should be able to document subjective and objective outcome measures. Once these criteria are met and no significant complications have been

reported, the cell line moves to the next stage. To move on to treating LCCL patients, at least 50 of the EICL patients should be at the 6 month follow-up stage and have no complications.

Late Clinical Cell Line (LCCL): This is an un-established stem cell line being used in a new tissue and is being used for early stage clinical treatments in 100-300 patients that are followed for a minimum of 6 months. The physician should be able to document subjective and objective outcome measures. Once these criteria are met and no significant complications have been reported, the cell line moves to the next stage. To move on to treating CG patients, all phases of the staging must be completed.

Clinical Grade (CG): This is an established cell line that has completed all stages above and is being used in patients in an unrestricted fashion. All patients being treated must still be entered into the ICMS Re-implantation Registry.

Summary Table of Clinical Staging for Cell Lines:

Clinical Staging Grade	Months of Treatment at the Clinical Stage	Number of Patients Treated in this Stage	Number of Patients at this Stage and Duration of f/u needed to begin Treating Patients in Next Stage	Preceding Stage and Duration in months of Follow-up Needed to Finish Stage
EICL	6	5-10	5-10 at 6 months	
LICL	6	20-50	20 LICL at 6 months	EICL-12
ECCL	6	50-200	50 ECCL at 6 months	EICL-18 LICL-12
LCCL	6	100-300	All phases of staging must be completed	EICL-24 LICL-18 ECCL-12
CG				

Exceptions

- A CG cell line does not have to pass the PICL/EICL/LICL process when used in a new tissue. With such use the cell line will be considered ECCL. The rationale is that for a homologous use, an autologous cell line that has shown durable safety in one homologous tissue type, is likely to show similar safety characteristics in other homologous tissue types as well. The cases would be entered into the re-implantation registry in the same fashion as other cases.
- Note that small culture changes made in an ECCL/LCCL or CG stage cell line that has been used with no complications and are in accordance with these guidelines (mimicking normal physiology) do create a “new cell line”, but this begins the staging in the ECCL stage. As an example of these small culture changes, this might include a change of basal media from A-MEM to D-MEM, a change in oxygen tension in culture, a change from serum free media to a documented, non-inductive FBS (Fetal Bovine Serum), or a change of adherence substrate from plastic to collagen with the concomitant switch from the use of trypsin to collagenase.

Certification of Clinical Cell Line Staging

Note that the ICMS Reimplantation Registry will be the final arbiter of the number of cases followed in each stage and if those cases have shown significant complications. In order for a cell line to be certified in any clinical stage, a letter is required from the ICMS Reimplantation Registry stating that the required number of cases have been documented for the requisite follow-up periods.

For the first 12 months after the acceptance by the ICMS membership of these guidelines, a clinical stem cell line can be “grandfathered” or accepted into the ICMS staging only if it:

1. Meets the definitions described herein (autologous, adult, minimal culture expansion, exposure to physiologic parameters in culture)
2. Has complications tracking data that meets the ICMS Reimplantation Registry’s standards.

The “grandfathered” line will enter into the clinical staging based on follow-up safety data as defined by the ICMS Reimplantation Registry with the issuance of a letter as described above. For example, a stem cell line with 50 patients in 12-24 month follow-up and 10 patients in 24-36 month follow-up that has shown no complications would enter at ECCL status. As end-point safety is the most important parameter, a cell line can be “grandfathered” as long as the line has current outcome data that meets the registry’s specifications. As an example, if a cell line has 100 cases with at least 24 month follow-up (all as single data points collected in the several months prior to ICMS certification), then the line can be “grandfathered” in the LICL stage.

INTERNATIONAL CELLULAR MEDICINE SOCIETY

ICMS

-  PATIENT SAFETY
-  PHYSICIAN EDUCATION
-  PEER OVERSIGHT

www.cellmedicinesociety.org

Using a Specific Cell Line in Practice

Cell Line Quality Assurance:

To ensure that any negative treatment outcome of an autologous stem cell culture process can be appropriately tested and tracked, ICMS recommends the use of a QA sample saved in cryo-storage (-150 C) for every completed cell culture. This is in addition to the exemplar lines stored as part of the ICMS Reimplantation Registry.

Clinical Use Recommendations:

As discussed above, once the stem cell line is established by its parameters, it must go through the clinical staging as described above. The ICMS guidelines do not permit the use of PICL, EICL, or PICL cell lines in routine clinical practice. ECCL and LCCL cell lines can be used in early clinical practice with the above noted restrictions. However, only “Clinical Grade” stem cell lines would have unrestricted clinical use with regard to numbers of patients allowed for treatment. Even patients being treated with a CG cell line must be entered into the ICMS re-implantation registry for long-term tracking and follow-up.

Significant Complications:

Significant complications are defined as an impairment of health or a condition of abnormal functioning that is directly caused by stem cell re-implantation. This does not include direct procedural complications such as infection, inflammation, tissue damage physically caused by the re-implantation, or manipulation of tissue. While these procedural complications should be recorded and could be used in the overall assessment of procedure safety, they are not considered as directly related to the stem cell line.

Basic Tenants of Clinical Translation

In addition to the above, the ICMS considers the following to be basic tenants of clinical translation:

- All research protocols using Early Investigational Cell Lines and Late Investigational Cell Lines should be approved by an Institutional Review Board.
- ICMS takes no position on how research is funded and due to the dire need for treatment options for patients approves the use of “pay for trial” type research.
- A blinded standard is not necessary for this phase of research. However, there should be measurement of both clinical outcomes and objective imaging or other objective changes.

We encourage all ICMS physicians to conduct blinded clinical trials. ICMS physicians will pool resources to allow these trials to be undertaken so that insurance reimbursement can be sought for therapies that pass this level of evidence.