International Cellular Medicine Society

**ICMS Cell Line Staging and Certification Process**
**Overview**

The goal of the Cell Line Staging and Certification Process is to assure patient safety and procedure efficacy. To that end, the ICMS has established a clinical translation staging and certification process for stem cell lines. This process monitors and validates the translation between cell line categorizations.

Every cell line will be classified and tracked according to its stage through the ICMS Re-Implantation Registry. To that end, every patient procedure utilizing cell lines must be registered and tracked within the Re-Implantation Registry. Through this Registry, the ICMS will document subjective and objective outcome measures and complications for each patient and cell line to determine the staging of each cell line.

The following staging categories have been developed by the ICMS for the purposes of clinical translation:

1. Pre-Investigational Cell Line (PICL):
    a. No animal data is available.
    b. These cell lines should not be used in humans until animal data is available.
2. Early Investigational Cell Line (EICL):
    a. An un-established stem cell line being used in a new tissue where several animal models, but no human data, exist that show efficacy and safety.
    b. EICL can be used in early stage human studies where 5-10 patients are treated and followed for a minimum of 6 months.
    c. EICL protocols requires approval of an Institutional Review Board
3. Late Investigational Cell Line (LICL):
    a. An un-established stem cell line being used in a new tissue and tested in humans.
    b. LICL can be used in larger numbers (20-50 patients) who are followed for a minimum of 6 months.
    c. 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.
4. Early Clinical Cell Line (ECCL):
    a. An un-established stem cell line being used in a new tissue and is being used for early stage clinical treatments.
    b. ECCL can be used in 50-200 patients that are followed for a minimum of 6 months.
    c. 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.
5. Late Clinical Cell Line (LCCL):
    a. An un-established stem cell line being used in a new tissue and is being used for early stage clinical treatments.
    b. LCCL can be used in 100-300 patients that are followed for a minimum of 6 months.

c. To move on to treating CG patients, all phases of the staging must be completed.

**6.** Clinical Grade (CG):

a. An established cell line that has completed all stages

b. Being used in patients in an unrestricted fashion.

c. All patients being treated must 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<br>LICL-12 |
| LCCL | 6 | 100-300 | All phases of staging must be completed | EICL-24<br>LICL-18<br>ECCL-12 |
| CG | | | | |

<u>Exceptions</u>

- 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

Upon acceptance of the successful completion of the required criteria for any stage, the ICMS will issue a letter of certification. No cell line will considered certified at any clinical stage without the issuance of the letter of certification.

The governing body of the ICMS Reimplantation Registry will be the final arbiter of cell line certifications. This body will have the sole power to grant certifications, set and adjust the number of cases followed in each stage, define significant complications and permit grand fathered acceptance of cell lines.

A clinical stem cell line can be "grand fathered" 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.

A cell line can be "grandfathered" as long as the line has current outcome data that meets the specifications of the ICMS. The "grandfathered" line will enter into the clinical staging based on follow-up safety data as defined by the ICMS with the issuance of a letter as described above.

## 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 requires 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 Re-Implantation Registry Guidelines.