

# EEBA STATEMENT ON STEM CELL APPLICATIONS IN THE TREATMENT OF OCULAR DISORDERS<sup>1</sup>

Venice, 22 October 2018

The research and innovation in the field of stem cells in ophthalmology have become challenging, with one product receiving a conditional marketing authorization in Europe (Holoclar, February 2015) and others (e.g. for the regeneration of the conjunctiva, the corneal endothelium, the corneal stroma, etc.) being under scrutiny for clinical feasibility. Despite these new developments, no revisions have been made to the EEBA “*Recommendations for Stem Cell Culture*” since their formulation in 2012.

Following the conditional marketing authorization granted to Holoclar by the European Medicines Agency (EMA) in 2015, ophthalmologists have now a stem-cell based treatment for adult patients with moderate to severe limbal stem cell deficiency (LSCD) caused by physical and chemical burns to the eyes. According to EU regulation 1394/2007, treatments based on Hospital Exemptions (HEs) are no longer allowed in those situations where a fully validated, centrally approved ATMP is available for the same indication in the same patient population. In Europe, therefore, ATMPs for LSCD prepared under the HE-rule can only be used in patients with different clinical indications from Holoclar label indication described above. Considering that LSCD is a rare disease with a reported frequency of 1-9/100.000, this is likely to lead to a very limited number of patients being treated in Europe with ATMPs that are different from Holoclar.

In addition, the safety and efficacy of *ex vivo* cultured LSC therapy outside Holoclar indication remain rather challenging as centres producing corneal limbal stem cell-based ATMPs use different techniques including the type of culture (from isolated cells or explant), presence of feeder-layer, scaffold (e.g. amniotic membrane or fibrin glue), cell culturing medium (i.e., synthetic or with animal-derived reagents) and quality control checks on the final product. Further variability is caused by the fact that each centre is treating patients with different degrees of LSCD (partial or total), the cause of LSCD can be different (congenital or acquired) and the source of the donor tissue (autologous or allogenic) could also differ. Therefore, the lack of a homogeneous treatment for patients with indications for LSCD outside Holoclar are likely to generate a plethora of different ATMPs prepared with the most diverse types of conditions/standards and authorized by national competent authorities for the most diverse types of patients and protocols. Efforts should be made in order to collaborate at EU level and reduce the uncertainty about the clinical safety and efficacy of those HE treatments.

A European registry of HEs across Europe for the treatment of LSCD outside Holoclar label indication would therefore be needed in order to:

- reduce variability and harmonize protocols;
- define clinical protocols;

<sup>1</sup> drafted by the EEBA Special Interest Group for “Advanced Therapy Medicinal Products” [Stefano Ferraro, Francisco C. Figueredo, Jesper Hjordtal, Neil Lagali, Gilles Thuret, Nadia Zakaria]

*The European Eye Bank Association (EEBA) is a technical-scientific organization comprising individual and institutional members from 27 countries. Founded with the simple objective of sharing information regarding eye banking, the Association is today the leading pan-national association in Europe dedicated to the advancement of eye banking and an authoritative reference point for eye banks wishing to work according to quality standards.*



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- define common criteria for success or failure;
- standardize follow-up outcomes and timelines;
- evaluate clinical efficacy and safety;
- perform health economics studies.

EEBA has recently joined the European Cornea and Cell Transplantation Registry (ECCTR), a European initiative co-funded by the Health programme of the EU and the European Society of Cataract & Refractive Surgery (ESCRS), in order to set-up an EU web-based registry in the field of cornea and to assess and verify the safety quality and efficacy of (new) human tissue and cell transplantation in ophthalmic surgery. As a side project, the ECCTR group is also drafting a web-based registry in which details of limbal stem cell transplantation procedures can be uploaded. Information about (1) characteristics of the recipient and donor eye, (2) previous clinical therapies, (3) surgery, (4) follow-up data and (5) patient reported outcome measures (PROMs) will be included in the registry.

The main recommendation to those within EEBA working on clinical applications of *ex vivo* expanded limbal stem cells for LSCD would therefore be to **input all the information related to cell culturing process, clinical phase and follow-up onto such a registry (or similar ones if available)**. This would greatly help:

- evaluating the clinical efficacy of each individual ATMP (other than Holoclar) prepared under HE on a larger target population;
- harmonizing the variability between countries regarding authorizations;
- finding alternative treatments to marketed products having more sustainable costs.

**A registry of limbal stem cell clinical applications could serve as a platform for a potential consortium to define the clinical safety and efficacy of treatments made with ATMPs different from Holoclar. This registry may provide to national competent authorities and the EMA evidenced-based data necessary to assess whether ATMPs prepared under the HE-rule are as safe and efficient (or not inferior to) as Holoclar and could therefore be a valid alternative (and potentially much cheaper for the national health systems across Europe) for treating patients with LSCD outside Holoclar label indications.**

In addition to *ex vivo* expanded limbal stem cells for LSCD, which is the most advanced technology in term of clinical applications, other ATMPs are being developed, e.g., for the regeneration of the conjunctival epithelium, the corneal endothelium, etc.

For the **conjunctiva**, the main issues are to define where precisely the conjunctival stem/progenitor cells are located and whether goblet cells can be differentiated *in vitro*.

For the **corneal endothelium**, many groups are actively pursuing the concept of regenerating the endothelium from induced pluripotent embryonic stem cells or from expanding adult endothelial cells. Because visual disability caused by corneal endothelial failure is by far more frequent than LSCD, and since the scarcity of donor corneas

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worldwide keeps increasing, corneal endothelial regenerative therapy is currently a challenging topic. Clinical trials have also been implemented (all in Japan, all by the same team) and cells injected in the anterior chamber of at least 35 patients, but results are yet to be published. The main issue is that the proliferative capacity of adult endothelial cells is very limited *in vitro*, declines with age and, more importantly, culture protocols need to be sought to reach a yield compatible with ATMP production. Critical quality control standards have also to be clearly defined to assess identity, purity, safety and functionality of the cells *in vitro*. Reliable preclinical tests, optimal surgical strategies for cell replacement and criteria for successful follow-ups have also to be defined.

In addition, several **other pilot studies of regenerative medicine** have been reported with clinical grade bone marrow- or cord blood-derive mesenchymal stem cells and with synthetic corneas and/or xenografts.

The field for these new applications is however at such early stages of development that drafting recommendations would seem premature. Special sessions, round tables or workshops should be held regularly at EEBA conferences in order to exchange information, define strategies and consensus papers. **Pan-European, EEBA-driven initiatives should be implemented in order to promote research studies aimed at moving these strategies and potential ATMPs into clinical applications.**



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