Advanced therapies for ocular surface reconstruction: from *in vitro* research to clinical trials

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The corneoscleral junction or limbus is the native niche for corneal stem cells (SC), especifically called limbal epithelial SC (LESC). Dysfunction of these cells (LESC deficiency syndrome) usually results in blindness and chronic pain by causing corneal opacity and persistent ocular surface inflammation, notably decreasing quality-of-life.

In these cases, corneal transplantation was the only option to recover vision, but a poor outcome was usually the rule due to the lack of LESC in the donor corneal graft. For the last 15 years, transplantation of pieces of limbal tissue directly from a cadaveric source or a living relative met good short-term results but only in some partial unilateral cases, failing (mainly due to immune rejection) in the more frequent cases of diffuse and/or bilateral disease. A more successful approach is the transplantation of *in vitro* expanded and cultivated LESC, an approach first described in 1997. Since then, progress has been made and at present transplantation of LESC has become the most successful therapy for LESC deficiency syndromes. This actually represents one of the first and clearest successes of regenerative medicine, as our work team is also demonstrating in an on-going clinical study. This study is being performed following good manufacturing practice (GMP) and good clinical practice (GCP) rules, and subsequently LESC are cultivated in a validated clean room (as mandated by the Spanish legislation, transposition of the European directive) and patients are followed under a strict clinical and surgical protocol. To date, 25 patients have been transplanted (mean follow-up, 9.2 months) with 80% global success, substantial quality-of-life improvement, and visual gain in 63% of patients. The 13 autologous and the 12 allogeneic transplants have presented similar results. The required immunosuppression for allogenic cases has been minimal, no sign of immune rejection has been observed, and additionally we have seen lower costs and less surgical morbidity. However, an important drawback remains, which is the dependency of donations in bilateral cases and the fact that an extra-surgical procedure is required in the only good-eye of a unilateral affected patient, increasing potential morbidity and sanitary costs. Therefore, an extraocular source of SC could be extremely valuable. As it is well known, mesenchymal stem cells (MSC) have a remarkably immunomodulatory capacity, and allogeneic transplantation of bone marrow-derived MSC (BM) has been successfully used for experimental ocular surface reconstruction. For this reason, we set out to demonstrate the hypothesis that the transplantation of BM-MSC cells is equal or superior to LESC transplantation through a randomized, double-masked clinical trial.