Innovative Medicines Initiative consultation: Facilitating the translation of advanced therapies to patients in Europe (Document reference: IMI2/OUT/2016-01321)

Submission from the European Eye Bank Association

The ***European Eye Bank Association*** (EEBA) is a technical-scientific organization comprising individual members from 84 eye banks from 24 European countries and beyond. 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.

Within EEBA, a **Special Interest Group for "Advanced Therapy Medicinal Products"** has recently been implemented to face the challenges set by the use of Advanced Therapy Medicinal Products (ATMPs) in ophthalmology.

We are thankful for having the opportunity to comment on this important document from Innovative Medicines Initiative (IMI). The scarcity of human donor cornea worldwide makes cell and tissue therapy a challenging solution for many patients with eye disorders and ATMPs have the potential to lead to better clinical outcomes, as compared to many existing and consolidated therapies available nowadays in ophthalmology.

Please find below our answers to the questions for which IMI and EFPIA are looking for input from scientific, regulatory, patient and healthcare systems communities.

1. **<u>Have the key challenges that can be addressed through collaborative, public private initiatives been properly identified?</u>**

When model systems are described (page 2) only animal models are described. However, we feel that *ex vivo* models should also be implemented, since for many tissues (e.g., the cornea) there are no suitable animal models.

When manufacturing is described (pages 3 and 4), evaluation of whether the "product" can be stored before use and shipped to distant centres across Europe should be carried out for any ATMP as early as possible during the preclinical development.

In addition to raw materials, it would also be essential to evaluate the scaffolds used to support cell growth and the presence of animal-derived products in the culture, as both critical for the quality of the ATMPs and ultimately of the clinical outcome.

2. **<u>Which of the proposed potential initiatives should be prioritised?</u>**

The regulatory issue is the main hurdle that needs to be prioritised if we aim for a safe, efficacious, but also effective process. Our view is that many obstacles are NOT facilitating the translation of advance therapies to patients as:

a) there is a complete lack of a clear interpretation of the regulations by the different member states (e.g., Do same cell types identify same ATMPs? Do same cell types, but different substrates/scaffolds identify same ATMPs?);

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b) marketing authorization is regulated at European level, while hospital exemption at national levels (AIFA in Italy; Special Manufacturer's Licence issued by the MHRA in the UK, etc.). This leads to uncertainty about the clinical application of ATMPs and the possibility for ATMPs prepared under the hospital exemption rule to be distributed within a member state when similar products have received the marketing authorization by EMA;

c) development and clinical application of ATMPs have always and are still driven by academic/hospital/non-profit organizations, which do not have the economic strength or the facilities/man-power to deal with the registration of a pharmaceutical product in Europe. Hospital exemption is therefore to be considered as the only way forward in many cases for many orphan diseases;

d) a number of university, hospital and non-profit centres throughout Europe have dealt since many years and are still dealing with orphan diseases and ATMP-based treatments. We feel that granting orphan drug designation exclusivity and marketing authorization to pharmaceutical companies, thus ignoring prior art and consolidated treatments is not going to help the patients and the National Health Systems. Prices for ATMPs developed by pharma industries are likely to be high and not easily accessible by all the healthcare providers, as public health systems and welfares are collapsing throughout Europe. Pharma industries are unlikely to gain revenues from ATMPs (huge costs, low numbers of patients) and might eventually drop such programs when considered not financially sustainable. Therefore, stopping academic/hospital/non-profit organizations from providing ATMPs on the basis of marketing authorizations and exclusivity for orphan diseases is eventually going to reduce dramatically the translation of advanced therapies to patients in Europe.

3. Are any areas missing?

Tissue engineered products. Many of the issues described are relevant and should apply not only to ATMPs, but to tissue-engineered products (TEPs) and medical devices made by tissue engineering techniques as well. Preparation of new treatments (medical devices) by de-cellularizing organs or tissues, or developing scaffold technologies (not containing cells or pharmaceuticals) are equally critical for meeting unmet medical needs as ATMPs. The framework on 'advanced therapies' should also encompass these products/devices, which face many of the same regulatory and production issues and challenges, although they lie outside the definition of 'ATMP'.

Treatment regimen and effect (page 5). Compared to traditional therapies, ATMPs are described as unique since one time/short term treatments can have long-term benefits. However, for example in ophthalmology, transplantation of autologous *ex vivo* cultured limbal stem cells has been shown to lead to partial successes and a second treatment has been carried out in some cases. As ATMPs are not to be considered definitive cures and/or miraculous, the possibility of partial success and the need for second dosing should be considered.

Study design. Reports and published data on the clinical use of ATMPs are often based on small cohorts, short follow-up times and different end-point assays for determining success/failure. Randomized controlled trials are difficult and rarely performed in cell-based therapies, therefore the need for well-defined and standardized patient registries would be the only alternative solution to be able

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to demonstrate long-term efficacy and safety of any given therapy. There is a need for standardization of patients enrolled in the studies, time frames for follow-up, assays used to define success/failure and more importantly outcome measures. A statistical analysis plan would also be needed to define better and in advance of any clinical result with ATMPs.

4. **What are the key European or national initiatives that IMI shall synergise with?**

IMI should synergise with EU platforms that are trying to develop European clinical registries or harmonize European guidelines on organ, tissue and cell transplantation. In ophthalmology, some Horizon 2020 – funded programs have already started (e.g., ECCTR and EuroGTPII) and similar initiatives should be backed up by IMI. Likelihood of success will surely be extremely challenging, as there are no records at both national and European levels on the use of ATMPs (both as hospital exemption product, marketed medicinal product or R&D experimental product). In addition, many of the data will be collected retrospectively and therefore rather limited information will be available. However, in the long-term, national (and if feasible European) registries will allow to characterize better the disease itself and the target patients and to analyze causes for success or failure, thus eventually reducing the variability and the lack of standardization that is commonly associated with the results obtained following the clinical application of ATMPs. The previous experience of the British, Swedish and Dutch registries for corneal transplantation is positive and should be followed.

In addition, given the complexity of the regulations underlying the manufacturing and clinical application of ATMPs, initiatives (backed up by IMI?) supporting educational programs should be developed both at national and European levels. Networking programs (e.g., COST initiatives) and specific Horizon 2020 could address these issues.

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