

Innovative Medicines Initiative (IMI) Consultation on Advanced Therapy Medicinal Products (ATMPs)

Response from the British Society for Gene & Cell Therapy (BSGCT)

Have the key challenges that can be addressed through collaborative, public-private initiatives been properly identified?

Overall, important barriers/challenges were identified but some hurdles are missing. Additional challenges are listed below (under missing areas).

Which of the proposed potential initiatives should be prioritised?

We believe that the “Concept Paper” summarises well the current key challenges. However, it is important to have strategic planning to prioritise the following:

- 1) Establish efficient GMP manufacturing technologies that can allow us to reduce the complexity, enhance capacity, access and increase the scalability. There is increased interest in developing the automated scale up platforms in universities, hospitals and SMEs but equipment must be matched with training of qualified staff, service costs and sufficient consumables to run them. It is very important we build expertise in this area with emphasis on strong understanding of the regulatory and the quality aspects.

Recommendation: development of European Hub for cGMP manufacturing with excellent capacity and industrial scalability

- 2) Culture systems for the large scale manufacture of vectors for clinical trials and commercialisation requires a substantial investment as each system requires careful optimization and validation, in compliance with EMA/National regulatory agencies.
- 3) Efforts and investment are needed to develop efficient producer cell lines. Transfection is widely used for vector production. However, this approach is susceptible to variation and the efficient transfection of large amounts of cells is considered a bottleneck/barrier in manufacturing for large clinical trials and commercialization of ATMPs. We therefore believe that stable producer cell lines provide scalability. The use of the producer cell lines may

‘To facilitate education, communication and sharing of knowledge and expertise.’

ultimately be more cost effective when larger volumes of product are needed and reduce variability, especially in late clinical phases and commercial manufacture.

- 4) There is an increase in regulatory scrutiny that does slow the development of ATMPs. European regulatory aspects for ATMPs are complex and not flexible in certain areas. “Fast track” processes are already established by FDA that could be a source of changes both for EMA and national agencies. Adjustments are probably needed in particular because of the recent refinement, safety and success clinical stories in the field and to allow us to keep up with other countries, US in particular.

*Are any areas **missing**?*

Here are some examples of important areas that were not addressed by the “Concept Paper”:

Gene-based therapies:

The main focus of the gene therapy section in this document is generic vectors and better purification processes, which we completely agree with. However, investment is needed in the development of a panel of optimal GMP cell lines- both constitutive and silenced (for silencing toxic transgene expression from certain vectors during production). At present there are limited GMP working master cell banks, almost entirely constitutive 293 based owned by individual companies. There are very few silencing cell lines (e.g. TetR regulated) and those that exist are proprietary to individual companies and hard to access for difficult to produce vectors, especially when working on translational projects in the academic sector. What is needed is access to available cell lines (plus some investment in cell line development) so that ideally a panel of constitutive and regulated cell lines are available for publically funded clinical trials, in order to allow small scale pilot studies to select best optimal cell lines for individual vectors before full GMP manufacture.

In addition to above, EMA/national regulatory agencies request for **full history** of MCB is another limitation of already small number of available cell lines for GMP clinical and commercial manufacture.

.....

Cell-based therapies

Overall, this is a broad field and issues are variable based on the type cells.

‘To facilitate education, communication and sharing of knowledge and expertise.’

BSGCT is a registered charity (1114715) and a company limited by guarantee (04964174).
Registered address: School of Biological Sciences, Royal Holloway, University Of London, Egham
Hill, Egham, Surrey, England, TW20 0EX

- Manufacturing: The main hurdle is that the change from a research grade reagent to GMP grade can affect the whole cell differentiation process. Several experiments including in vivo efficacy validations need to be performed to confirm that the protocols still work under GMP compliance.
- Cell sorting and cryopreservation: positively selecting the wanted cells is associated with the risk of losing many cells during the process. Cryopreservation is also an issue in some areas. For instance cryopreservation of dopaminergic cells requires dimethyl sulfoxide (DMSO) however concerns were raised on whether DMSO could be tolerated by the cells in the brain? Investment/efforts are needed to improve the cell sorting and cryopreservation
- Regulatory: This vary between countries and harmonisation of regulatory aspects is needed for better guidance of product development from discovery to commercialisation.

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

UK Regenerative Medicine Platform - for which the MRC are expecting to issue new calls for consortia working in Round Two, sometime around the end of this year.

Government initiatives: e.g. Cell and Gene Therapy Catapult

G-Force PD: a global initiative in coordinating stem cell-based dopamine treatments for Parkinson's disease

Regulatory agencies: We think we shouldn't limit this synergy to Europe but instead reach out to other regulator bodies (e.g. FDA) to create a harmony re regulatory aspects allowing easy and fast progress from discovery to commercialisation of ATMPs.

General comments/feedback

- Advanced therapy medicinal products (ATMPs) is hugely broad field. Do you think focus on key areas would lead to success?
- Enthusiastic support for the idea of a database of Hospital Exemptions and other small studies
- Cautions re the role of the empty virus particles, I don't think enough is known about the basic biology here
- The discussion about cell therapies within the "Concept Paper" seems reasonable - clearly though as ever there needs to be a recognition of the needs for supporting work on the underpinning science. Clearly the gene editing approach has huge implications for making sets of isogenic lines with specific disease related mutations for in vitro disease modelling.

'To facilitate education, communication and sharing of knowledge and expertise.'