Advanced Therapy Medicinal Products

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Executive summary

Advanced Therapy Medicinal Products (ATMPs) are innovative and complex medicines which can potentially be used to treat a variety of human health issues, including cancers (such as leukemia and melanoma), neurodegenerative diseases (such as Huntington's and Parkinson's diseases), inherited diseases and autoimmune diseases (such as diabetes, multiple sclerosis and rheumatoid arthritis). They are particularly important for severe, rare, or chronic diseases where conventional approaches have proven to be inadequate. The number of patients treated with specific ATMPs, however, is still very low.

Universities already play an important role in ATMP development, but their role could be improved, made larger and more prominent, if specific hurdles were addressed. In this paper, we outline possible ways in which this could be done. These include:

- Improving interactions with, and help provided by, support organisations, such as EMA, industry and other universities, to cover better the whole product development pathway and to ensure support (including financial) at all stages of development.

- Universities should focus on new innovative products that address an unmet medical need and have a high chance of success and on products which are unlikely to be attractive to industry.

- Retaining the Hospital Exemption[1], but harmonising its application, improving its assessment and using it only in product development or for products not suitable for Marketing Authorisation. A registry should be developed to record information on ATMP use under the Hospital Exemption.

- Improving transparency, both in ATMP trials and in the use of the Hospital Exemption, which will help organisations active in this field to learn from others' successes and failures.

LERU hopes that the actions in this paper will lead to the development of new therapeutic options, improved links with the pharmaceutical industry and, most importantly, to better patient access to these innovative medicinal products.

1 See section 4 for an explanation of the Hospital Exemption

1 ATMPs and university research

Advanced Therapy Medicinal Products (ATMPs) are innovative and complex medicines which are based on somatic cells[2], genes or tissues. The variability of products covered by this definition is high, including cell suspensions, viral vectors, plasmid DNA or mRNA, engineered tissues and combinations thereof. ATMPs can be defined as a new class of advanced medicines and can potentially be used to treat a variety of human health issues, including cancers (such as leukaemia and melanoma), neurodegenerative diseases (such as Huntington's and Parkinson's diseases), inherited diseases (such as immunodeficiency syndromes) and autoimmune diseases (such as diabetes, multiple sclerosis and rheumatoid arthritis). They are particularly important for severe, rare, or chronic diseases where conventional approaches have proven to be inadequate or where there is room to improve particular treatment strategies (e.g. administering the genetic information encoding the protein rather than the protein itself). The number of patients treated with specific ATMPs, however, still is very low.

This paper has been developed by the League of European Research Universities (LERU), an association of 23 leading research-intensive universities in Europe. Several LERU universities are very active in the ATMP field and have faced difficulties in bringing novel ATMPs to patients. This paper gives recommendations for improving the ATMP environment in university medical centres. LERU hopes that this will lead to the development of new therapeutic options, an increased involvement of pharmaceutical industry and to a better patient access to these innovative medicinal products.

Some examples of ATMPs which are currently commercially available are Holoclar, which uses human corneal epithelial cells to treat the degeneration of corneal tissue resulting from chemical or physical burns to the eye, and Kymriah and Yescarta, where lymphocytes of patients with leukaemia are genetically modified to recognise the patient's own cancer cells and destroy them.

2 Somatic cells are those cells from a body which are not reproductive cells

ATMPs are centrally regulated at the European level through Regulation (EC) No. 1394/2007 of the European Parliament and of the Council of 13th November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No. 726/2004.

A Marketing Authorisation (MA) is needed for ATMPs to be commercially available. The European Medicines Agency's Committee for Medicinal Products for Human Use makes a recommendation for MA to the European Commission which makes the final decision. ATMPs are very different to conventional medicines, often having complex manufacturing processes, orphan indications[3] and tailored production, and are therefore often seen as products with a low commercial value and/or a high commercial risk [1]. As of May 2019, 14 ATMPs have been granted a MA for the European Economic Area (EEA)[4], however, four of them already have been withdrawn from the market for a variety of reasons. An alternative route for patient access in Europe is through the Hospital Exemption (HE), which allows the use of ATMPs under the supervision of a medical practitioner, on a non-routine basis, and in restricted circumstances, in a single member state.

Universities are a major player in the ATMP field. Most ATMPs are initially developed by universities and more than half of the clinical studies with ATMPs in Europe were sponsored by universities [2-4]. In part, this is because university medical centres have the necessary disease-specific expertise, the capacity for innovative research and direct access to donor and patient material [1]. Universities dominate early stage (phase I/II) clinical research, while industry is more involved in late stage clinical development [3, 4]. However, while universities already play an important role in ATMP development, their role could be improved, enlarged and more prominent, if the hurdles they encounter were addressed. Indeed, while many clinical studies are performed, only a few products are further developed and reach the patient. This paper will discuss the hurdles and seeks to outline how these can better be addressed.

3 Orphan indication means an indication with a limited number of patients (rare diseases) https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview

4 These are outlined in table 1 in the Appendix

2 Focusing ATMP development at universities

Universities experience significant hurdles during product and clinical development of ATMPs. These largely relate to a lack of financial support, the speed of innovation, a lack of regulatory expertise and knowledge regarding product development practices [5, 6]. In addition, a study on the benefit/risk assessments of ATMPs submitted for MA showed that there were often concerns related to the quality and design of clinical studies [7, 8]. In the section below, we consider how universities and other players in the public sector can focus on the development of ATMPs. These include:

- Working on the product development pathway with the necessary specialists to bring ATMPs to the patient more effectively by starting the whole process earlier on in the development of that therapy (see section 2.1).
- Developing ATMPs that are unlikely to be adopted by industry (see section 2.2).
- Focusing on ATMPs with a high chance of success and that require specialist scientific knowledge (see section 2.3).

2.1 Working on a complete product pathway with the necessary specialists to more effectively bring ATMPs to patient

Successful drug development, particularly in the complex area of ATMPs, requires an integrated team effort, where – early on – all stakeholders come together to form a translational drug development team. Such a team would include: pre-clinical developers; clinicians; experts on intellectual property; pharmaceutical experts of quality / good manufacturing practice (GMP) / product development / quality assurance; regulatory experts; project managers; health technology assessment experts and patient organisations. The goal of such a team would be to create an integrated strategic development programme, encompassing pre-clinical and clinical development, and requiring collaboration initially at a local level, but ultimately at a member state and/or EU-wide basis.

Traditionally, when involved in product development, universities have taken a step-by-step development process rather than starting with the end-product application in mind (a target product profile[5] [9]). This can result in them spending too much time on refining aspects of the production process which at the end seems not to be translatable to a GMP grade environment, for example due to a lack of suitable raw materials for GMP-grade production. Researchers need to be aware of the requirements of GMP-grade production, discuss this early on in the development team and direct the protocol according to this. Universities should be encouraged to implement translational drug development teams, and to use a risk-based approach from the beginning to make decisions based on the target product profile. An example in this is the Translational Research Office (TRO) established at University College London (UCL)[6]. The TRO, which is populated with industry-experienced drug developers, has established a portfolio of ATMPs with well-thought-through project plans and target product profiles. Due to the innovative nature of ATMPs, the manufacturing process and product composition may be refined during product development, but this is much more difficult during clinical development.

Adaptive trial designs[7] are increasingly considered for use, particularly for rare diseases and in the field of oncology. In universities in particular, clinical trials are frequently designed on an individual basis rather than as part of an integrated clinical development programme with a defined overall objective. When approaching clinical trial design for ATMPs, it is important to first establish what clinical data is needed from the study, and the level of detail required. It is advisable to consider regulatory aspects of ATMPs under development early on, prior to clinical trial design as regulatory guidance is key for successful development. Asking for advice before the funding application to ensure the development project is on the right track will enhance the success of funding applications. In addition, patients and patient organisations should be encouraged to get involved in early stage clinical trials, for example by developing patient-reported outcomes.

5 A target product profile or a quality target product profile forms the basis of design for the development of the product
See also https://www.ema.europa.eu/en/documents/scientific-guideline/note-guidance-pharmaceutical-development_en.pdf or
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080593.pdf)

6 https://www.ucl.ac.uk/translational-research/

7 A clinical trial that evaluates a treatment by observing participant outcomes (and possibly other measures, such as side-effects) on a prescribed schedule, and modifying parameters of the trial protocol in accord with those observations

To be able to improve product development at universities, (financial and infrastructural) support for all stages of the development pipeline is necessary with reasonable timelines attached. This support needs to be flexible and applied to a number of projects. To ensure agility, a critical mass should be established, according to the predicted pipeline of activity, which will enable a sharing of knowledge and best practice. Where possible (part of) the activity will be covered by grants. However, in addition, the support requires financial underpinning allowing continuity of staff employment as well as career development and the ability to provide support at the critical time before an application for funding is submitted.

Recommendation to universities, the European Commission, industry, National Competent Authorities and ATMP regulators:

Ensure support (including financial) at all stages of development for implementing integrated clinical development programmes that begin early on in the therapeutic development of the product

2.2 Universities should focus on the early development of new innovative ATMPs to be picked up by industry in late development and develop ATMPs that are unlikely to be taken up by industry

As previously discussed, universities play a leading role in the early development of ATMPs but a more limited role in late stage development. However, both early and late stage development cannot be seen as being independent of each other. Industry has the experience of late development and should mainly be responsible for this and for registration studies. Nevertheless, the role of universities in late stage development certainly has to be considered and probably should be extended in specific cases.

Universities should focus on the early development of innovative new therapies or in providing products to patients with an unmet medical need with products that will not be picked up by industry for reasons of low commercial value and/or a high commercial risk. When shown to be successful following a previous clinical trial, such products should, after careful assessment, be made available to patients in specialised medical centres. In this case, the late phase product and clinical development should be done by university medical centres to develop a product which meets the quality requirements for clinical use.

A way to enable this is to create partnerships between universities, charitable funders and regulators. An example of this is the CRUK Centre for Drug Development[8]. Creating such capabilities embedded within universities would empower universities to negotiate with industry (see section 3.3). On the other hand, these products, developed by universities without the intention of obtaining a MA, are appropriate for use under the HE guidelines (see section 4.2).

Recommendation to universities:

Focus efforts on early phases of new innovative ATMPs and ATMPs that meet an unmet medical need and/or are unlikely to be taken up by industry

8 https://www.cancerresearchuk.org/funding-for-researchers/our-research-infrastructure/our-centre-for-drug-development

2.3 Focusing on ATMPs with a high chance of success

Although many clinical studies with a lot of different products are performed, only a few ATMPs seem to reach the market/patient and many clinical studies are done without any long-term follow-up of the treated patients. Assessing the potential success rate of a product is challenging and should be done in a detailed and systematic way. Assessment from a university-based perspective should at least include an assessment of unmet medical need, innovation, quality of preclinical development, possible clinical safety and efficacy and potential for reimbursement, (a strategy which already is adopted by University College London's TRO). These assessments would be aided significantly by the publication of such data (see section 5.2) [10-12], and could also be used as a call for further investments in research and development processes. They might benefit from an EU initiative for the development of an independent university-led panel of experts to evaluate ATMPs as this could raise the overall success rate of ATMPs being developed.

Recommendation to the European Commission:

Develop an independent panel of experts advising on the potential impact and route to the clinic of ATMPs under development

Recommendation to universities, industry and publishers:

Publish data on all clinical studies of ATMPs including long-term follow-ups and also those trials that failed on their primary end point and define the appropriate tool to collect data from them (see also section 5.2)

3 Improving interactions between ATMP stakeholders

ATMPs pose a unique challenge to researchers in the university setting, both from a product and clinical development perspective. Although the manufacture and administration of ATMPs frequently takes place at a single centre, it is rare that a single centre has the experience and expertise to efficiently take the product through all clinical phases without additional input and support. In particular, regulatory knowledge and experience is frequently lacking in a university setting. LERU suggests the following:

3.1 Improving interactions between universities, regulators, and/or EMA to improve effectiveness of product research and development

LERU strongly encourages university-based researchers involved in ATMP development to interact with the national competent authorities and/or EMA early on in the product development pathway, and to maintain continuous engagement throughout the clinical development process. The EMA offers a range of advisory services and incentives to support the development of ATMPs. Scientific advice may be requested from the national competent authorities and/or the EMA at any stage of the development process. In our experience, it is often better to explore first national advice as this is often easier, cheaper (or free) and can be relatively informal. In addition, this can be appended to funding applications. Although traditionally the EMA has had more tools in place for support of small and medium sized enterprises than university researchers, additional support for universities has recently been established. University researchers are advised to go to the EMA to discuss scientific matters via the EMA's Innovation Task Force[9], who offer meetings for free, and maintain a priority status for universities. It is important for participants to realise that financial resources still need to be found in order to be able to attend these meetings. In addition, extended supportive and financial concessions from the EMA which are specific for universities could contribute enormously to the field and lead to enhanced patient access.

Recommendation to the European Commission:

Extend financial concessions offered to universities

Recommendation to the European Commission and universities:

Improve (awareness of) the range of advice channels and supportive tools available to university-based ATMP developers

9 https://www.ema.europa.eu/en/documents/other/mandate-european-medcines-agency-innovation-task-force-itf_en.pdf

3.2 Fostering the development of university research networks focused on ATMP development

University medical centres involved in the development of ATMPs frequently represent a heterogeneous group of stakeholders who work, with regard to product development, in relative isolation from a national and international perspective. However, in view of the highly specialised expertise required for ATMP-related research and product development, there is significant value in the establishment and maintenance of university research networks with a specific focus on ATMP development. This offers the potential for the sharing of relevant expertise and knowledge in product development, establishment of international specialised clinical trial networks and the opportunity for integrated sub-specialised researcher training. In addition, manufacturing facilities and activities in such networks will aid in training of personnel involved in manufacturing like pharmacists and other scientists. Examples of this are the Dutch-Flemish Belgium ATMP working party in which information on ATMP manufacturing and GMP ATMP issues is shared between university and not-for-profit ATMP manufacturing sites, The Centre for Advanced Medicinal Products in Sweden (which provides assistance for the development of ATMPs), and UCL's ATMP Therapeutic Innovation Network. National centres of excellence could be used to help support such a European network.

Recommendation to the European Commission:

Launch an initiative to bring together university research networks focused on ATMP development

3.3 Improving coordination between universities and industry

As previously discussed, universities mainly have a role in the early development of ATMPs with a more limited role during later stages of development. However, both early and later stages of development are dependent on each other. Industry has the experience of late development and should mainly be responsible for this work and registration studies. The links between university and industry should be improved, which amongst others should be done by establishing public-private platforms, like for example REGMEDXB[10] or ADVANCE(CAT)[11]. However, the role of universities in late stage development certainly has to be considered and probably should be extended on specific issues. Universities may need to be more empowered to conduct late stage development and thereby building the next generation of capabilities and expertise in this area. It is essential that this is done in partnership with industry. Thus, it will be important that universities play an active role in the negotiation process at the stage where the product is being transferred from universities to industry, to facilitate cost-effective product development and to secure any future revenue to support the next generation of ATMPs. It is important to note that university contract departments need to have access to additional training to handle these types of negotiation.

Recommendation to universities and industry:

Develop better links between universities and industry to improve the transfer of products from the university to industry. For example, by setting up a public-private partnership platform for ATMPs

10 https://regmedxb.com

11 https://www.advancecat.net/

4 The Hospital Exemption

The Hospital Exemption (HE) is defined in the European Regulation ((EC) No 1394/2007), as an ATMP '*which is prepared on a non-routine basis according to specific quality standards and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient*'.

The HE is regulated at a member state level, and is only allowed when used on a non-routine basis in a hospital setting for a specific patient with specific quality criteria under the responsibility of a physician. As HE must be authorised by a national competent authority, its adoption in EU member states is very variable. ATMP products produced under the HE can only be used within the member state where they are produced. The use of the HE has drawn some criticism as being a route which could compete with commercial ATMP product use.

In this paper, we consider 1) how we could move towards a more harmonised HE environment across Europe and the benefits that could bring, 2) how a voluntary registry of ATMP uses could be developed, and 3) in which conditions the HE should be used.

4.1 Implementing voluntary-based standardisation of the HE across Europe

Ideally, the HE should be harmonised between EU member states. However, differences in interpreting the Regulation between the different EU member states makes it difficult to harmonise and compare treatments and data between countries. The European Commission has instigated a consultation process with the member states on the HE[12]. However, voluntary-based standardisation procedures can be promoted beginning with a few countries inside the EU. LERU can play two important roles in this initiative: ATMP-production centres at LERU universities could put together

12 https://www.ema.europa.eu/en/documents/other/european-commission-dg-health-food-safety-european-medicines-agency-action-plan-advanced-therapy_en-0.pdf

common approaches and standardise production and clinical procedure, and LERU can campaign for the EU and the national competent authorities to facilitate standardised production and clinical procedures and eventually harmonise HE legislation among EU countries.

Recommendation to universities:

Develop common approaches to standardise production and clinical procedures for the HE

Recommendation to National Competent Authorities and the European Commission:

Standardise production and clinical procedures for the HE

4.2 Redefining the use of the HE in universities

The use of the HE has been subject of intense discussion. Industry is particularly critical about the use of the HE due to concerns about possible competition with marketed drugs. However, the HE seems to be the only route to allow patients access to some types of ATMPs. In order to prevent undesirable competition with similar marketed drugs, as well as to ensure patient access to therapies, LERU considers it important to redefine or to better specify how the HE should be used within universities. LERU believes that the HE should be used in two different scenarios:

A. During product development

During product development, the HE can be used to bridge the continuation of treatment of patients between different phases of clinical development or to treat patients outside a clinical study. It may also be used during early stage product development where manufacturing protocols are still fluid and rapidly evolving, before moving to the more rigid late phase clinical trial procedures.

B. For products not suitable for Market Authorisation

The HE should be a way to allow patient access for ATMPs that have been shown to be successful but which will never become available on the market. This includes products with no or low commercial value, which will never go for MA, as well as those products which have obtained a MA but have been withdrawn from the market due

to commercial reasons (in particular for autologous products). To be able to keep providing these therapies to patients it is important that there is a possibility for extension of the HEs granted (after assessment of safety and efficacy of the treatments given).

Patient safety should be prioritised whenever patients are treated under an HE. With regard to this, we would like to emphasise that a mature assessment for approval of an HE is of significant importance and should include at least quality and safety data available for the product. Implementation of such an assessment is essential to be able to use the HE within universities.

Recommendation to National Competent Authorities and the European Commission:

Redefine the use of the HE

Recommendation to National Competent Authorities:

Implement a mature assessment on at least the quality and the safety of the product for HE applications

5 Supporting actions

5.1 Training for academic ATMP developers to be available and be part of the university career

The training of university-based ATMP developers, and regulators involved in ATMP evaluation at the national and European level, is key to the successful development of ATMPs in a university-based setting. Such training should ideally be integrated with university career development, and should be encouraged with the involvement of national and international funding bodies. Such training can take the form of on-campus training, on-line courses or combinations thereof. Additionally, integrating the training with that of industry partners would create an ideal opportunity for interaction and collaboration between universities and industry. Training related to ATMP development could be incorporated in PhD, PharmD and MD study programmes relating to ATMP development. Additionally, ATMP specific training courses may be required as part of MD and PharmD license re-training programmes through cross border collaboration. Summer schools may offer another route to deliver such training.

Recommendation to universities:

Explore how ATMP development training can be incorporated into medical and post graduate training and re-licensing programmes, e.g. by organising summer schools

5.2 Improve transparency in ATMP development

Although the field is very active, the sharing of knowledge is often lacking, which can have detrimental effects on product development. Transparency in the field should be improved, so that we can all learn from each other's successes and mistakes. Universities should set an example in this and should start to make this data publicly available. This should include, but not be limited to, results from clinical studies including data on the long-term follow-up of patients including with products that have failed their primary end point and/or had limited clinical effect, useful information for

the field obtained from scientific advice or evaluation on the HE performed by a competent authority, and the costs of the development and manufacturing of ATMPs. Creating transparency and clarity on costs will hopefully also lead to better financial support for the development of ATMPs in universities and a more equitable reimbursement of the treatment with ATMPs of patients. Publishing data from all clinical trials of ATMPs including those that failed to meet their primary endpoints would help reduce duplication of effort, promote a sound assessment of potential products and will certainly prevent spending a lot of time and money on products with a low potential for success and a high change of failure.

Recommendation to universities:

Develop and implement a voluntary transparency agreement whereby data from all clinical trials, including costs, should be published in a voluntary registry or should be available in a public journal or domain

5.3 Create a voluntary registry of HE uses

At present, there is a lack of transparency with regard to the use of the HE. Data from treatments carried out under HE procedures that are not conducted within clinical trials are not available to the public or other researchers or clinicians. This is in contrast to clinical trials that need to be public and transparent for the scientific, clinical and patient community. Improving the transparency of the HE procedure within each country and between countries will facilitate standardisation of the protocols and data. This would also help patients and patient organisations know about what HE possibilities exist and which hospital they can go to for treatment.

The HE does not fall under the remit of either the EMA nor the national competent authorities. The active sharing of information could however, be set up by university sponsors who could organise voluntary registers in an open-access database such as the EU clinical trials register[13], the EBMT patient registry[14] or via the Notify project[15]. A voluntary registry would not only facilitate the access to strategies and data but should also provide clearer evidence for efficacy of products used in the HE as well as treatments that have been unsuccessful, which in turn, should avoid unnecessary

13 https://www.clinicaltrialsregister.eu/about.html
14 https://www.ebmt.org/ebmt-patient-registry
15 http://www.who.int/transplantation/tra_notify/en/

treatments. A patient registry of ATMP use would also provide data to help reimburse ATMP treatment in some countries by allowing the clinical data to be 'published'. Close collaboration between universities and regulators is advised in order to identify what costs need to be considered for reimbursement.

Patient or treatment registries have been also recommended for ATMPs by the EMA in a recent document published in collaboration with the European Biopharmaceutical Enterprises[16]. In that document, the EMA and European Biopharmaceutical Enterprises recommended establishing academic and industry registries "*…in the hands of specialised data platform providers (guardians), with patients owning the data (users) and other stakeholders having access...*". An example of such a registry is the cellular therapy registry of EBMT[17], which has recently harmonised the registration of many different cellular therapies across the globe and could be used for products used under HE. The general accessibility of data to other stakeholders in this field will be key to its success with a carefully designed transparent data release process which will allow for the extraction of valuable data without harming new products at an early stage with premature conclusions. Key elements would include a desire to not collect complete data sets such as all product details and all side effects but to carefully distil a data set that reflects key assets, without losing important information, which should be done very carefully so as to avoid bias in the selection of data. In addition, such not-for-profit registries could become a valuable tool for long term data collection across diseases and capture many different ATMPs. The backbone of existing registries could be considered as potential templates for ATMPs under HE.

Recommendation to universities:

Use a voluntary registry to record information on ATMP use under both the HE and in clinical trials and explore the use of already available registries

16 http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/02/WC500221149.pdf
17 https://www.ebmt.org/ebmt/news/ebmt-receives-regulatory-qualification-european-medicine-agency-ema-use-its-patient

6 Conclusions

University medical centres play an important role in ATMP development and utilisation and are the ideal conduit through which scientific developments which improve ATMPs can be introduced into patient care. However, LERU believes that the environment for ATMP development in university medical centres could be further improved. It is perhaps timely for universities to reflect on how they can operate more effectively in the ATMP area, and for the regulators and other policy makers to identify how they can better support the valuable services of universities in this area. This paper has provided some ideas on how this could be facilitated.

LERU believes that universities have an important role in complementing the industrial sector in the ATMP area. University medical centres should maintain an important role in early stage ATMP development and in delivering to the patient ATMPs which are likely to have a low chance of being adopted by industry (for example withdrawn products or those products with limited commercial value). As a result, it is essential to retain the HE platform which provides a vital way in which much-needed ATMPs can be administered to patients. However, there should be greater transparency as to what is being done through this route.

The ATMP field is, at present, rather fragmented. In addition, the high variability of products covered by the ATMP definition does not lend itself to generalities and a case-by-case product development plan is often needed. Improving coordination between the different players in the ATMP field will greatly help improve the effectiveness of ATMP development and, as a result, improve patient care. By improving transparency – for example, over the use of the HE – ATMP trials and development / utilisation costs could reduce duplication of effort, make it easier for (all) ATMP developers to identify products with a higher chance of success, help patients and patient organisations to identify possible centres for treatment, and provide costs to aid reimbursement claims. Improving links with industry can help fill the knowledge gaps and help smooth the transition between the universities and a saleable product. University-based ATMP developers should also be more aware of the support available from the national competent authorities and EMA throughout the ATMP development and use process.

Finally, the career paths of university-based ATMP developers could be improved substantially and training on ATMPs (development, commercialisation and delivery in the hospital setting) should be part of medical training schemes. Academic scientists working on ATMPs should be recognised, not only for their research, but for the vital role that they play in developing treatments for patients, which in general gets little reward leading to a clear disadvantage in terms of acquiring funding and also academic visibility.

7 Recommendations

In this section, we summarise the different recommendations suggested in the paper and those institutions that should be leading on these.

Universities should:

- Ensure support (including financial) at all stages of development for implementing integrated clinical development programmes that begin early on in the therapeutic development of the product
- Focus efforts on early phases of new innovative ATMPs and ATMPs that meet an unmet medical need and/or are unlikely to be taken up by industry
- Publish data on all clinical studies of ATMPs including long-term follow-up including those trials that failed on their primary end point and define the appropriate tool to collect data from them.
- Improve the awareness of the range of advice channels available to university-based ATMP developers
- Develop better links with industry to improve the transfer of products from the university to industry. For example, by setting up a public-private partnership platform for ATMPs
- Develop common approaches to standardise production and clinical procedures for the HE, e.g. by organising summer schools at LERU universities
- Explore how ATMP development training can be incorporated into medical and post-graduate training and re-licensing programmes, i.e., by organising summer schools at LERU universities.
- Develop and implement a voluntary transparency agreement whereby data from all clinical trials, including costs, is published in a voluntary registry or should be available in a public journal or domain
- Use a voluntary registry to record information on ATMP use under both the HE and in clinical trials and explore the use of already available registries

Recommendations

The European Commission should:

- Ensure support (including financial) at all stages of development for implementing integrated clinical development programmes that begins early on in the therapeutic development of the product
- Develop an independent panel of experts advising on potential impact and route to the clinic of ATMPs under development
- Improve awareness of the range of advice channels available to university-based ATMP developers and supportive tools available to university-based ATMP developers
- Extend financial concessions offered for universities
- Launch an initiative to bring together university research networks focused on ATMP development
- Standardise production and clinical procedures for the HE
- Redefine the use of HE

ATMP regulators should:

- Ensure support (including financial) at all stages of development for implementing integrated clinical development programmes that begins early on in the therapeutic development of the product
- Redefine the use of HE
- Implement a mature assessment on at least the quality and the safety of the product for HE applications

National Competent Authorities should:

- Ensure support (including financial) at all stages of development for implementing integrated clinical development programmes that begins early on in the therapeutic development of the product
- Standardise production and clinical procedures for the HE
- Redefine the use of HE
- Implement a mature assessment on at least the quality and the safety of the product for HE applications

Recommendations

Industry should:

- Ensure (financial and other) support at all stages of development for implementing integrated clinical development programmes that begins early on in the therapeutic development of the product
- Publish data on all clinical studies of ATMPs including long-term follow-up including those trials that failed on their primary end point and define the appropriate tool to collect data from them
- Develop better links with universities to improve the transfer of products from the university to industry. For example, by setting up a public-private partnership platform for ATMPs

Publishers should:

- Publish data on all clinical studies of ATMPs including long-term follow-up including those trials that failed on their primary end point and define the appropriate tool to collect data from them

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9 Appendix

Product	Orphan Designation	Year of issue of MA	Therapeutic indication	Active substance
Chondroselect	No	2009 *	Cartilage defects of the knee	Autologous cartilage cells
Glybera	Yes	2012 #	Familial lipoprotein lipase deficiency (LPLD)	Adeno-associated viral vector for gene delivery
MACI	No	2013 #	Cartilage defects of the knee	Matrix applied characterised autologous cultured chondrocytes
Provenge	No	2013 *	Prostate cancer	Autologous PAP-GMSCF activated peripheral blood mononuclear cells
Imlygic	No	2015	Melanoma	Oncolytic viral therapy
Holoclar	Yes	2015	Corneal lesions	Autologous human corneal epithelial cells containing stem cells
Strimvelis	Yes	2016	Severe combined immune deficiency	Genetically modified autologous CD34+ cells
Zalmoxis	Yes	2016	Graft versus host disease after allogeneic stem cell transplantation	Genetically modified autologous T cells
Spherox	No	2017	Cartilage defects of the knee	Spheriods of autologous matrix-associated chondrocytes
Alofisel	Yes	2018	Rectal Fistula – Crohn's disease	Adipose derived allogeneic mesenchymal stem cells
Yescarta	Yes	2018	Relapsed of refractory B-cell lymphoma	Genetically modified autologous T cells
Kymriah	Yes	2018	B-cell leukaemia or B-cell lymphoma	Genetically modified autologous T cells
Luxturna	Yes	2018	Retinitis Pigmentosa	Adeno-associated viral vector for gene delivery
Zynteglo	Yes	2019	Transfusion-dependent β-thalassaemia	Genetically modified autologous CD34+ cells

* withdrawn;
\# expired and not renewed

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