Health by Advanced Therapies

D2.6
Strategy paper on biomaterial developments and composite products

Public

Delivery date: 31/07/2020

Lead beneficiary: UZH (Partner 02)
Lead beneficiary reallife: UMINHO (Partner 10)

Table of contents

1. Deliverable's description

Advanced Therapy Medicinal Products (ATMPs) can be defined as a new class of living drugs and can potentially be used to treat a variety of human health issues, including neurodegenerative diseases (such as Huntington's and Parkinson's diseases), inherited diseases (such as immunodeficiency syndromes), autoimmune diseases (such as diabetes, multiple sclerosis and rheumatoid arthritis) and cancers (such as leukaemia and melanoma). Therefore, new generation tissue engineering (TE) and composite products are an important pre-requisite in the area of regenerative medicine and prospective ATMP-based biomedical interventions. ATMPs are designed out of biomaterial structures composed with e.g. somatic cells, genes, bioactive molecules or tissues. The variability is quite numerous, including cell suspensions, viral vectors, plasmid DNA or mRNA, engineered tissues and combinations thereof. The development of new tissue engineering and composite products is particularly important for severe, rare, or chronic diseases where conventional approaches have proven to be inadequate or where there is room to radically improve existing treatment strategies (e.g. administering the genetic information encoding the protein rather than the protein itself). Unfortunately, the number of patients treated with specific ATMPs is still very limited.

TE products are regulated at the European level through either Regulation 2007/1394 or through Regulation 2017/745, of the European Parliament and of the Council pertaining respectively to ATMP and medical devices, depending on their classification. In both cases, specific authorization pathways are followed to attain market entry. For example, in the case of ATMP, the European Medicines Agency's Committee for Medicinal Products for Human Use makes a recommendation for market authorization (MA) to the European Commission which makes the final decision. 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 leukemia are genetically modified to recognize the patient's own cancer cells and destroy them (see also figure 1).

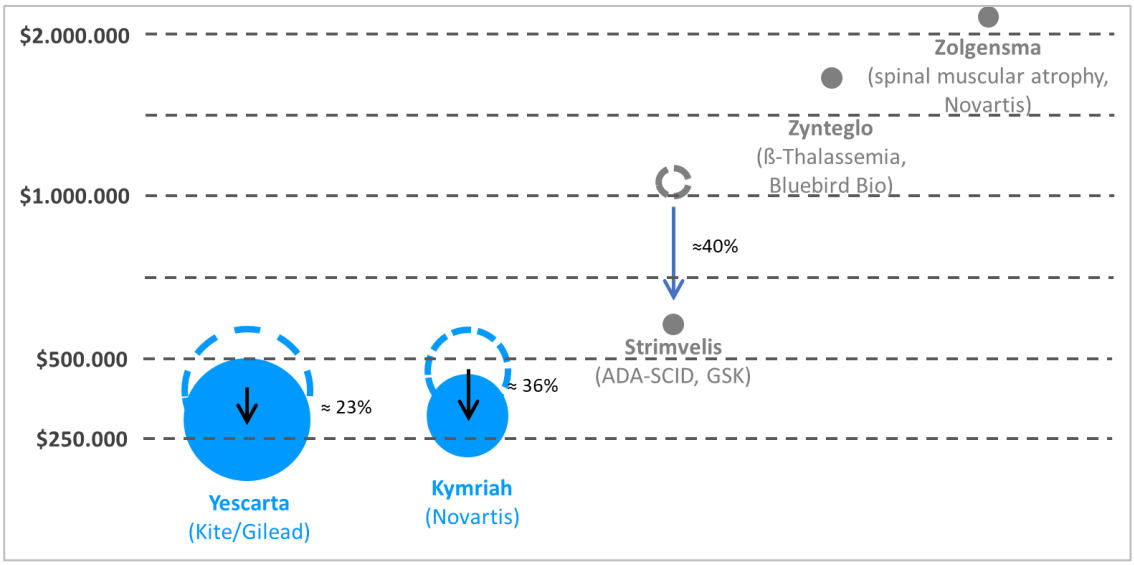

Figure 1: Pricing of current gene therapies. Costs for therapeutic cell products are illustrated in the figure as well as relative market sizes (indicated by the different contents of the circles). CAR T cell products (in blue) are compared to other gene therapy products (Strimvelis, Zynteglo, Zolgensma; in grey). Dashed circles indicate the initial prices of Yescarta, Kymriah and Strimvelis; arrows and percentages indicate drops in market prices in Germany. Initially in 2018, Novartis charged USD 475,000 for Kymriah and Gilead UDS 373,000 for Yescarta. Since then, prices have dropped significantly, i.e. in Germany to USD 304,000 for Kymriah and USD 311,000 for Yescarta (Siegmund-Schultze, 2019) – which equals pricing reductions by 36% respectively 23%.

ATMPs are very different from conventional medicines, often involving complex manufacturing processes and personalized production. They are frequently seen as products with a limited commercial value, as it is for therapies addressing rare diseases, and/or a high commercial risk. As of May 2019, 14 ATMPs have been granted a MA in the European Economic Area (EEA), however, four of them were already withdrawn from the market for a variety of reasons. An alternative route for patient access to ATMPs in Europe is through hospital exemption, 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 EU member state. Universities are a major player in the ATMP field. Most TE and composite products are initially developed by universities and more than half of the clinical studies with ATMPs in Europe are proposed and sponsored by universities. In part, this can be explained by the fact that university medical centers often possess the necessary disease-

specific expertise, the know-how for innovative research and direct access to donor and patient tissues and cells. In the case of ATMP, universities dominate the early stage clinical research (phase I/II), while industry is more involved in late stage clinical development (phase III/IV). In this document, we discuss the current hurdles and seek to outline how current limitations can be more effectively addressed, mainly focusing on ATMP and combination products. The aim of this strategy paper is to outline prospective developments in TE and composite products in order to catalyze their MA and assess the potential of the RESTORE consortium in stimulating and accelerating this process.

2. State of the art

New generation TE and composite products are central in the area of regenerative medicine and ATMP-based biomedical interventions. Currently, TE and composite products are based on a wide range of synthetic and natural biomaterials. The fundamental constituents of TE and combination products can be classified as:

i) Cells, which can either be used for autologous / allogeneic therapies or for the production of TE extracellular matrix *in vitro*. Examples of cell sources are mesenchymal stem cells (MSCs), MSC-like cells, placenta, umbilical cord, adipose tissue, pluripotent stem cells (PSCs), insulin-producing cells or induced pluripotent stem cells (iPSCs);

ii) non–cellular components such as cell-derivatives (extracellular vesicles/exosomes), secretomes, naturally-occurring / synthetic scaffolds, composite products (cells combined with natural / synthetic / hybrid scaffolds), and

iii) *in vivo* gene therapy (delivery of genes).

A large variety of *in vitro* and *ex vivo* culture systems are available for both experimental small-scale and industrial large-scale productions, such as bioreactors, embedded sensors for chemo-mechanical online monitoring, and embedded micro-nano actuators for physical-chemical stimulation. Advanced fabrication procedures, e.g. bio-printing, scaffolds- and organoid

manufacturing (and combinations thereof) are widely established or are in late developmental phases.

Currently addressed indications include skin repair, cartilage, bone, muscle, spine, cornea, vascular grafts, oesophagus, trachea, bladder, neurological lesions and myocardial/epi-cardial patches for the treatment of ischemic diseases and heart failure, or beta cells.

New composite products are being launched but also continuously improved regarding their properties. ATMPs are very complex structures, the key qualities of biomaterials and composite products must include e.g. that they are: easily modified (to combine effectors), provide reasonable mechanical/functional properties, bacteriostatic, anti-viral, fungistatic, non-toxic, non-allergic, haemostatic, and biocompatible.

Developments in tissue engineering products that have heathcare relevant applications include e.g. cell derivatives, hydrogels, matrixes (tissue engineered), films, hydrocolloids, foams, peptides/proteins. The virtually endless possibilities of TE products have the potential to address many of the currently unmet clinical needs in severely debilitating conditions.

3. Challenges and Limitations

Many clinical trials of TE and composite products have been conducted or are ongoing, involving e.g. MSC/MSC-like cells, iPSCs, and gene therapy. Despite that, only a limited number of products have completed clinical translation.

This is due to a series of hurdles encountered during the development phase, including among others:

1. Ensuring patient's safety and consistent quality for TE products, such as those based on *in vitro* / naturally occurring extracellular matrices
2. Reproduction of native-like composite tissues *in vitro*, such as scaffolds for orthopaedic applications (e.g. bone-cartilage-bone)
3. Capability and capacity to fabricate fully functional human tissues of large dimensions on a large scale
4. Implant/transplant-integration in the recipient-site, such as in the case of cardiovascular implants
5. Adequate in-process controls and product release criteria
6. Stability/kinetics *in vivo* and biodegradation-related safety aspects

7. Scale up-, automation, and scale out strategies

Beyond the numerous technology specific hurdles, we believe that four additional key challenges generate a bottleneck for clinical translation of TE and combination products. As mentioned earlier, universities dominate early stage clinical research whereas industry is more involved in late stage clinical development however, while universities already play an important role in TE and composite product development, their contribution to clinical translation of these products could be considerably improved. The RESTORE consortium aims to catalyze this process by considering the following points:

- TE and composite products require **highly interdisciplinary** expertise and team efforts, where all stakeholders cooperate to accelerate the transition to clinical application.
- To cover all aspects of product development from initial concepts to clinical translation scientists and engineeres should be connected with an interactive and integrated network of clinicians, study nurses, investors, experts on intellectual property (IP), experts on regulatory affairs and quality management / assurance, business developers and project managers. These professional figures are often not adequately connected within academic institutions, leading to time- and cost-intensive delays in the development processes. Only when highly organized networks of specialists from various interdisciplinary fields work together can the translational hurdles be reduced to a minimum.
- **Universities typically lack expertise in product and clinical development**. Therefore, quality management principles and product/process validation are often neglected during the development of innovative technologies. Moreover, other aspects of technology transfer need to be taken into consideration, such as fund raising, IP, market understanding, market entry, industrialization.
- **Regulatory hurdles:** Due to the innovative technologies used in TE, one of the major difficulties in the translation of TE products is the understanding of the adequate classification of the product and the development of the regulatory strategy. For the same

reason, identifying the applicable guidelines and applicable standards for these products it is often not obvious, and requires early interactions with the regulatory bodies.

4. Putative solutions

In order to foster clinical translation of TE-based products, the following putative solutions are recommended:

i) Strengthen the collaborative effort between research institutions, health care institutions and industry, with complementary expertise and infrastructures in large consortia

ii) Enhance the exchange of knowledge and expertise among the partner institutions

iii) Research and healthcare infrastructures should be adapted to the manufacturing and regulatoric requirements of TE products

iv) Regulatory and quality standards should be revised to embrace breakthrough innovative technologies such as TE, and to streamline their pathway to MA

v) Regulations and quality standards should be harmonised among the different EU-member states

5. Challenges for RESTORE

Formation of a translational ATMP development team:

Effective TE and composite product development, requires an integrated team effort. Particularly for ATMPs, all stakeholders should work together to form a translational drug development team (TDDT). Such a team should comprise, among others, GLP-trained preclinical developers, GCP-trained personnel, IP experts, quality and regulatory experts, product / process developers, project managers, health technology assessment experts and patient organizations. The goal of such a team would be to generate an integrated strategic ATMP development program, encompassing pre-clinical and clinical product development. Patient organizations should be encouraged to get involved in early stage clinical trials, e.g. by developing patient-reported outcomes. To further strengthen the partnership value creation environment, interdisciplinary entrepreneurship and innovation programs should be offered for adequate education and training of researchers, covering the essential aspects outlined above for promoting the successful

creation of spin-off companies (IP, development of a business plan, regulatory affairs and negotiation strategies, etc.).
Only in highly collaborative networks of specialists from various interdisciplinary fields, can translational hurdles be condensed to a minimum in a reasonable timeframe.

Strengthen academic and research infrastructures

In research projects, universities and research institutions typically adopt a step-by-step development process rather than starting with the end-product application in mind (a target product profile). When attempting to transfer research projects to GMP-compliant infrastructures, common difficulties include the lack of suitable raw materials for GMP-grade production, the lack of adequate access to GMP facilities (e.g. cleanroom) and to clinical sites/personnel. Researchers need to be involved in a collaborative environment in which experts in the requirements for GMP-grade production of test samples are involved in the early stages of development to ensure compliance of research with current regulations. Universities and research institutions should be encouraged to implement TDDTs, and to use a risk-based approach from the initial stages to make decisions based on the target product profile. The Wyss Zurich, a joint accelerator of the University of Zurich and ETH Zurich was founded in 2015 with the aim of closing the gap between basic research and clinical translation of novel technologies. In the case of regenerative medicine / TE projects, the accelerator provides support with industrial expertise in the design, analysis, business strategy and quality management, contributes to financial coverage of translational research / first-in-man clinical trials, and provides access to GMP manufacturing facilities. Due to the innovative nature of such products, the manufacturing process and product composition may be refined during product development, but this is much more difficult during clinical development. Adaptive trial designs are increasingly considered for use, particularly for rare diseases and in the field of oncology.
In universities and research institutions, the clinical trials are frequently designed on an individual basis rather than as part of an integrated clinical development program with a defined overall objective including interdisciplinary aspects from the very beginning. The design of clinical trials should start by adequately defining the objectives and endpoints of the trial, the study subjects.

Additionally, in the clinical translation process, regulatory aspects should guide the whole product development process.

The Clinical Trials Center (CTC) of the University Hospital in Zurich is part of the Research and Education Office of the University Hospital Zurich. The CTC has been operative since 2006 and is an ISO 9001:2015 certified institute with the necessary expertise to support academic projects in the field of translational and clinical research. All clinical research projects must be conducted in compliance with the GCP principles. GCP define international ethical and scientific quality standards for the design, conduct, documentation and management of trials which involve the participation of human subjects. Compliance with GCP provides public assurance that the rights, safety and wellbeing of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki. Professional medical and paramedical CTC personnel provide research teams with consultations and support during all stages of a clinical project. Next to the provision of project related support, the CTC provides a comprehensive educational program, with the emphasis on the theoretical and practical training of persons involved in the planning and conduct of clinical research projects. GLP is a set of principles intended to assure the quality and integrity of non-clinical laboratory studies that are intended to support research / marketing authorization for products regulated by government agencies. Despite the importance of GMP, GLP and GCP, their widespread implementation in academic sites is still in its infancy.

In order to catalyse the translational process of TE and composite products, academic institutions should implement adequate infrastructure and quality management systems. In order to exchange GMP, GLP and GCP-services and/or to increase the number of certified laboratories, the members and partners within the RESTORE consortium are in positions which can enable them to help to implement such standards and share existing experience and knowledge.

Definition and harmonisation of regulatory and quality requirements

As mentioned previously, the classification of TE and combination products, including ATMP is often challenging. In particular, when assessing whether a product falls under the ATMP definition, the following aspects must be determined: (i) whether or not a manipulation of a living material is considered substantial, and (ii) whether the product can be qualified not only as medicine but also as medical device, cosmetic, or tissue and cells. Although this process might

appear easy to navigate, for some newly developed TE and composite products, the classification frequently depends on an arbitrary decision of the regulatory authority.
The Committee for Advanced Therapies (CAT), located in Amsterdam, The Netherlands, is the European Medicines Agency's (EMA) committee responsible for assessing the quality, safety and efficacy of ATMPs. The CAT further classified ATMPs as (i) innovative products comprising gene therapy medicinal products (GTMPs), (ii) somatic cell therapy medicinal products (sCTMPs), or (iii) TE products – depending on their characteristics, mode of action, and intended function. For example, while sCTMPs are intended for the prevention, diagnosis, and/or treatment of diseases via pharmacological or metabolic actions, TEPs are used for regenerating, repairing, or replacing a human tissue. Future amendments of existing regulations should provide investigators and stakeholders a defined framework as per the applicable classification criteria and regulatory pathways for TE products.

Another example is given with regard to the hospital exemption according the European Regulation No 1394/2007. The purpose of the hospital exemption is to allow clinical use of an ATMP without marketing authorization. The hospital exemption can be used in a clinic when there is a high unmet medical need and an individual patient under the exclusive professional responsibility of a medical practitioner. The hospital exemption is regulated at a national level, and is only allowed when used on a non-routine basis in a hospital setting for an individual patient with detailed quality standards under the accountability of a clinician. Since a hospital exemption must be authorized by a national authority, its implementation in EU member states is therefore very variable. Although on one hand, ATMPs produced under the hospital exemption can only be used within the national member state where the material has been manufactured, on the other hand the use of the hospital exemption has created some criticism as being an alternative route, which could compete with commercial use of biomaterial based ATMPs. Ideally, the hospital exemption should be harmonized within the EU. However, differences in interpretation of the regulation between the different EU member states makes it difficult to harmonize and compare treatments and data between countries. RESTORE could contribute to the standardization process at two levels: first, TE-production centres at RESTORE institutions could put together common approaches and standardize production and clinical applications; second, RESTORE can campaign for the EU and the national competent authorities to facilitate

standardized production and clinical procedures to eventually harmonize hospital exemption legislation among European countries.

6. Summary

ATMPs, which include certain TE and composite products, can be defined as a new class of medical intervention and can potentially be used to treat a variety of human health issues. ATMPs can be developed out of TE and composite products based on e.g. somatic cells, genes or tissues. Therefore, new generation medical tissue engineering and composite products are an important pre-requisite in the area of regenerative medicine and prospective ATMP-based biomedical interventions. The development of new ATMPs are particularly important for numerous severe or chronic diseases where conventional approaches have proven to be inadequate or where there is room to improve particular treatment modalities. However, the number of patients treated with specific ATMPs, is still in its infancy. Most TE and composite products are initially developed by universities and research institutions and more than half of the clinical studies with ATMPs in Europe are sponsored by them.

Three main challenges are identified as forming a bottleneck preventing patients from accessing time-efficient development of prospective tissue engineering and composite product-based interventions:

(i) The development of ATMPs is a highly interdisciplinary task, it requires an integrated team effort, where, early on, all stakeholders come together to form a translational drug development core team. However, these requirements are often not adequately recognized and professionalized within academic and research institutions and create time- and cost intense delays in the development processes.

(ii) The lack of quality controlled infrastructures (e.g. ISO, GMP)/validated processes (e.g. GLP), financial support, regulatory expertise (e.g. GCP), and knowledge regarding product development, means that institutions face substantial hurdles during product and clinical development.

(iii) During the application process of an ATMP, the appropriate classification of the requested product, not only for the applicant but also for authorities and notified bodies is imperative. Thus, the early classification of an ATMP is not only a matter of regulatory compliance, but may also influence an investigator's approach and business model. However, for particular TE and new

composite products it is sometimes difficult and very time intense to identify which guideline (e.g. ISO 13485, ISO 10993, and EU-GMP) is relevant for the requested manufacturing process and how the intervention can be classified. Further, differences in interpreting the regulation between the different EU member states makes it difficult to harmonize and compare treatments and data between countries. This is forming an additional limitation and bottleneck in comparison to to non-EU competitors, e.g. USA and China.

As putative solutions to the previously discussed challenges and limitations, the following recommendations are given: In order to foster biomedical interventions in the area of prospective ATMP-based therapies, i) the exchange of different disciplines should be encouraged, ii) academic infrastructure should be adapted to the requirements desired, and iii) quality guidelines should be (re-)defined, homogenized and implemented among the partnership involved in the development process and within the EU memberstates.

Putative solutions could be established and employed by member organizations of the RESTORE consortium. In order to catalyze the translational process during development of biomedical products, academic institutions should further focus on the setup of such institutions. In order to exchange GLP, GMP/ISO or GCP-services and/or to increase the number of certified laboratories. The members and partners within the RESTORE consortium could implement and share existing experience and know-how. (iii) ATMP-production centers at RESTORE institutions could put together common approaches and standardize production and clinical applications. The member institutions of the RESTORE consortium can campaign and advocate at the EU and the national competent authorities to facilitate standardized production and clinical procedures and eventually harmonize legislation among European countries by serving as a leading, showcase example of pan-european networking research and industrial infrastructures able to routinely develop and translate new ATMPs into the clinic.