

The expanding role of the clinical haematologist in the new world of advanced therapy medicinal products (ATMPs).

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Summary

Advanced therapy medicinal products (ATMPs) represent the current pinnacle of “patient-specific medicines” and will change the nature of medicine in the near future. They fall into three categories; somatic cell-therapy products, gene therapy products and cells or tissues for regenerative medicine which are termed “tissue engineered” products. The term also incorporates “combination products” where a human cell or tissue is combined with a medical device. Plainly many of these new medicines share similarities with conventional haematological stem cell transplant products and donor lymphocyte infusions as well as solid organ grafts and yet ATMPs are regulated as medicines. The development of these medicines has remained predominantly in academic settings and within specialist centres. However, with the advent of commercialisation of dendritic cell vaccines, CAR-T cells and genetically modified autologous haematopoietic stem cells to cure single gene-defects in β -thalassaemia and haemophilia, the widespread availability of these therapies needs to be accommodated.

Uniquely to ATMPs, the patient or an allogeneic donor is regularly part of the manufacturing process. All of the examples given above require procurement of blood, bone marrow or an apheresate from a patient as a starting material for manufacture. This can only occur in a clinical facility licensed for the procurement of human cells for therapeutic use and this is likely to fall to haematology departments either as stem cell transplant programmes or as blood transfusion departments to provide under a contract with the company which will manufacture and supply the final medicine. The resource implications associated with this can impact on all haematology departments, not just stem cell transplant units, and should not be under-estimated.

Keywords –

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Clinical trial

Introduction

The advent of the EU Medicines Directive in 2001 [2001/83/EC] created a new class of medicines which contained or consisted of human cells or tissues and which have been termed Advanced Therapy Medicinal Products or “ATMPs”. ChondroCelect, a mesenchymal stromal cell product to repair damaged cartilage led the way in the EU as the first ATMP to obtain a manufacturing authorisation for supply as a licensed medicine and was followed by Glybera, Provenge and Holoclar. Apart from Glybera, each of these requires procurement of patient cells, as a starting material, in a hospital setting which is licensed for therapeutic cell procurement. Provenge was the first autologous dendritic cell vaccine to become licensed and, although it subsequently failed commercially due to low efficacy, other DC vaccines are already in late phase trials. Holoclar, a complex construct of autologous limbal stem cells on an engineered scaffold for corneal repair, is the first combination ATMP to obtain an EU marketing approval. Late phase, commercial clinical trials of gene-modified autologous haematopoietic stem cells for correction of congenital single gene defects, autologous monocyte-derived dendritic cell vaccines for a variety of cancers, CAR-T cells and cell-based cancer vaccines are all underway, as are early phase trials of complex 3-D regenerative medicine constructs by academic groups and commercial developers.

The 2001 Medicines Directive and the Advanced Therapy Medicinal Products regulation [Regulation 1394/2007] which followed in 2007 introduced the concept of two different types of therapeutic cells; “substantially modified” versus “minimally manipulated” or “non-substantially modified”.

“Minimally-manipulated” or “non-substantially modified” cells and tissues are not medicines but are “cell or tissue therapies” such as conventional haematopoietic stem cell transplants and the distinctions will be highlighted below.

ATMPs are medicines and are divided into three broad classes - “somatic cells”, “gene therapies” and “tissue engineered products” although even this regulatory classification is not straightforward and often confusing. Somatic cell medicines can range from allogeneic anti-viral T cells to treat post-transplant EBV lymphoma to mesenchymal stromal cells (MSC) used for suppression of acute graft versus host disease. Gene-modified CAR-T cells are categorised as “gene therapy products” yet their mode of action is not by in vivo genetic modification. Moreover, suspensions of autologous or allogeneic MSC used for enhancing endogenous repair for cartilage defects are “tissue engineered products” rather than “somatic cells” despite the fact that they may have been isolated and manufactured in exactly the same process as MSC defined as a “somatic cell therapy” above. Moreover, MSC combined with a scaffold for production of an engineered trachea are “combination ATMPs” and not “tissue engineered” products!

These difficulties are compounded further by the similarity between ATMPs and “routine” stem cell transplant products where the distinction between “minimally-manipulated” cell or tissue therapy, versus an ATMP, is often very challenging and sometimes even inconsistent between EU member states. This is compounded by the sheer heterogeneity of ATMPs, especially for autologous, or patient-specific allogeneic, products which, following the success of CAR-T cells in early trials, is a burgeoning field.

Taking the UK as an example, the MHRA is the agency with the statutory right to determine whether the product is an ATMP or a cell therapy which would then be regulated under the

EUTCD. This is not a trivial decision since even minimally manipulated therapies might be classified as an ATMP if the cells will be used “non-homologously” i.e. not intended to be used for the same essential function(s) in the recipient and the donor – even when the cells are used autologously. A good example of this regulatory razor are CD133+ bone marrow derived progenitor cells isolated by immunomagnetic selection, such as CliniMACS. If these cells are used for HSCT then they are unlikely to be classified as “substantially modified” since direct cell separation and concentration without cell culture is “non-substantial manipulation” according to the ATMP Regulation 1394. The same cells when injected into a coronary artery, or into cardiac muscle to enhance regeneration post myocardial infarct, have been classified as an ATMP based on their 'non-homologous' use, i.e. the CD133+ cells will be injected into an anatomical site which an EMA expert committee has decided is not a physiological site for those cells and thus the risk of the therapy warrants regulation as an ATMP.

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000301.jsp&mid=WC0b01ac05800862c0]

The regulation of substantially modified cells in 2001 was rapidly followed by the EU Tissues & Cells Directives [2004/23/EC] to regulate non-substantially modified therapies in 2004. These include routine HSCT products such as cryopreserved autologous haematopoietic stem cells (HSC) and even CD34 selected HSC for allogeneic HSCT since both procedures are regarded as minimal manipulation. The EUTCD is the legislation with which all HSCT haematologists are familiar since it is the basis of the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (Q&S Regulations). Under these Regulations, the Human Tissue Authority (HTA) licenses and inspects establishments that undertake the procurement, testing, processing, storage and distribution of human cells and tissue for therapeutic use and this authority extends to licensing procurement of human cells and tissue for manufacture of an ATMP. This piece of legislation requiring licensing of procurement of human cells and tissues is unique to the EU. The US Federal Drug Administration regulates the manufacture and supply of cell-based medicines and the Australian Therapeutic Goods Administration regulates ATMP equivalents as “biological medicines” but neither yet requires licensing of the clinical site where the patient or donor cells/tissues are procured.

Abbreviations:

ATMP	Advanced therapy medicinal product
BE	Blood establishment
EUTCD	EU Tissues and Cells Directives
DI	Designated Individual responsible for an HTA licence
HSC	Haematopoietic stem cell
HSCT	Haematopoietic stem cell transplant
HTA	Human Tissue Authority
JACIE	Joint Accreditation Committee ISCT/EBMT for HSCT programmes
MHRA	Medicines and Healthcare products Regulatory Agency

What sorts of cells and tissue might haematology teams need to supply?

In 2013 the UK Department of Health established a Regenerative Medicine Expert Group (RMEG) to report on the regulation, logistics and reimbursement of ATMPs in recognition of the importance of this new class of medicines. The report [RMEG 2014] concluded that the UK NHS Blood & Transplant facilities are well placed to support the procurement of cells and tissues as starting materials for ATMP manufacture. Whilst this is true of procurements from normal volunteer donors it is unlikely to apply to patient-derived cells and tissues which will need to be procured in a hospital setting.

Given the diversity of ATMPs, the procurements can include surgical biopsies, surgical resections, bone marrow aspirates or full harvests, moderate volume blood samples, or apheresates from mobilised or non-mobilised patients or donors (table 1). In some cases they may be residual cells from a haematopoietic stem cell transplant (HSCT) product such as are being used to produce anti-viral T cell products from allogeneic donor HSCT.

At UCL all three types of ATMP for academic and commercial clinical trials are manufactured. The donor-derived cells and tissues used for these products include: small volume bone marrow aspirates for mesenchymal stromal cell isolation and seeding of decellularised tracheal scaffolds [Elliott et al 2012], surgical biopsies for epithelial cells and fibroblasts, muscle biopsies for mesangioblasts for engineered oesophagus products, as well as clinical apheresates from autologous and allogeneic donors. In all cases supply agreements have been established with third party clinical sites for the procurement of cells and tissues under their existing Human Tissue Authority (HTA) procurement licence and under the authority of the local HTA Designated Individual (DI). Sometimes these agreements are simple and are designed solely to meet the obligations of each party under the EU Tissues and Cells Directive (EUTCD). In others, they become complex legal contracts taking many weeks to get signed off by the local hospital administration and involving legal fees to draft.

For a busy DI in a clinical HSCT unit to take on the paperwork to facilitate non-HSCT procurement is challenging; especially for a clinical service which has nothing to do with haematology patients. Even setting up the collection of a small bone marrow aspirate for the isolation of bone marrow MSC in an out-patient clinic for a regenerative medicine product requires new paperwork and often new training records, plus a supply agreement with the end user and a process to report any serious adverse events or reactions (SAEARs) which may occur after the starting material has left the procurement facility. The complexity is increased if procurement activity is extended outside of the HSCT unit, for example to cover collection of a tumour resection from an operating theatre by surgeons and theatre nurses who have never worked under a regulated quality system.

Organising the logistics and calculating the costs of procurement and supply to the end user, and then invoicing of the end user for the service are all tasks which require resourcing in order to provide a service for the supply of starting materials.

Why has this situation arisen?

Whatever the ATMP and whatever the cell or tissue required for its manufacture, the procurement is a licensable activity in the EU. In the UK this is regulated mostly by the HTA although, in the case of blood cells, the MHRA may regulate under the Blood Establishment

licensing procedure. Each EU member state has its own regulatory system (www.agora-gmp.org) and local rules apply.

Procurement of patient or donor cells and tissues is licensed to ensure appropriate consent is obtained, appropriate screening of the donors for infectious disease is performed and full traceability of the donor and the donation is in place. Whether the cells/tissues are to be used for a routine transplant or as the starting material for manufacture of an ATMP is irrelevant from a haematologist's perspective. The donor or patient cells must be procured by an HTA licensed establishment and the donor must be tested for the infectious disease markers set out in the HTA Directions. In all licensed establishments the HTA procurement licence is overseen by a DI and, in most cases (s)he is within, or associated with, the haematology department as part of the HSCT programme. The procurement system to support a routine HSCT service is generally established and validated to support the procurement of a limited number of types of cell, in a very defined clinical area under the control of the DI. However, the procurement licence and the quality system which supports it are valuable assets to hospitals facing the challenges of supporting clinical trials and routine use of ATMPs; consequently DIs will be faced with requests to supply a range of cells and tissues in the near future [Chabannon et al 2014]. Making an existing HSCT procurement system work to support the regulated procurement of a wide range of different tissues and cells from across the hospital is challenging and potentially expensive.

Is this an opportunity or a risk?

All changes present opportunities and risks and the field of ATMPs presents some of the greatest changes to delivery of medicine of the past 20 years. For haematologists involved in transfusion or transplantation, these new medicines represent huge opportunities because of their established expertise in procurement and traceability of human cells; but the risks of providing an academic collaboration or even a commercial service to participate in the manufacture of a medicine need to be recognised.

One of the greatest challenges of running an HSCT programme is covering the "back office" costs of the apheresis unit and the stem cell processing laboratory; this is why so many HSCT programmes have chosen to outsource at least one of these operations to a third party provider. Many of these costs are also incurred by blood transfusion departments in maintenance of their MHRA licence as Blood Establishments (BE). With the advent of academic or commercial supply of procurement services to ATMP companies, there is a need to set up a costed service with a billing structure which could be used to support the quality manager, DI and the apheresis team with additional resources. This could, in turn, subsidise the Blood Transfusion laboratory or HSCT programme to some degree. Haematology departments without HSCT programmes may even consider using their existing quality systems supporting the blood transfusion services to enable them to obtain HTA licensing for procurement and testing of cell and tissues simply to support this burgeoning demand or to add procurement to their existing BE licence.

Supply of any service comes with risks, not least the expectation of the purchaser whether academic or commercial. The EU Clinical Trials Directive raised the bar for compliance with Good Clinical Practice by universities and hospitals involved in academic, early phase trials. The provision of cells and tissues to academic colleagues for ATMP manufacture requires a

contract which is no less complex than one to supply cells to a major pharmaceutical company for a clinical trial, and the expectations of the trial office will be the same. Scheduling patients referred by other clinical teams for an apheresis slot in a busy HSCT practice or arranging a small volume bone marrow aspirate in the Haematology Out-Patient Clinic can be challenging; even more so when the end user demands a specific date in order to meet a downstream manufacturing deadline. This might require extension of the operating hours of the apheresis unit or out-patient clinic, with the additional costs being met by the academic or commercial contractor. When providing costs as part of an academic grant application these additional costs need to be addressed.

It is essential to establish the product quality characteristics which the end user requires before entering into an agreement to supply. ATMPs will never be inexpensive medicines and the liability for the final product must remain with the manufacturer. Already there are anecdotal reports that some hospitals are seeing this potential liability as a reason not to supply starting materials for commercial clinical trials. The supply agreements should delineate the specific responsibilities of each party. For example, for starting materials the donor screening for infectious disease markers falls under the EUTCD (or EU Blood Directive if obtained under this legislation). In the UK this must be carried out by an establishment licensed by the HTA or MHRA for donor testing. If the screening misses an early HIV infection and the product is manufactured and released who is responsible for the cost of the resultant product recall and destruction or, worse, the liability to the patient if it has been administered already?

The agreed product characteristics should ensure that the clinical site only provides the end user with starting material with sufficient cells of adequate viability and that are free from microbial contamination for the downstream manufacturing process. The traceability must be guaranteed and records retained for 30 years in accordance with legislative requirements. The tests used to show that the starting material meets these pre-determined standards need to be qualified and, in the case of donor screening and product sterility tests, fully validated. It is worth considering outsourcing sterility testing to an MHRA licensed testing facility rather than requiring in-house microbiology departments to go through formal validation of their sterility assays for your products. Alternatively, the supplier can pass the sterility testing of the starting material to the manufacturer of the ATMP. If so, then the third party agreement between the HSCT procurement service and the ATMP manufacturer must require that the procurement DI is informed of any products which are contaminated so that (s)he can report any associated SAEAR to the HTA and oversee the route cause analysis or the MHRA if procured as a Blood Establishment.

How can a procurement service be established?

As with all changes this will require consultation and a business case for investment (table 2). Existing HSCT programmes will have set up procurement policies and procedures for JACIE compliance and to meet the requirements of the HTA regulation. These may be reviewed with hospital legal advisors regarding their suitability for provision of a procurement service to third parties, so that standardised templates are created which cover regulatory demands and specific requirements of the hospital to define the limits of

liability. This could substantially reduce the demands on the DI when requests are made. At the same time a limited training scheme could be created for staff who need to be included within the procurement licence on a short term basis. For example, nurses or junior doctors who may be expected to take a bone marrow aspirate for MSC isolation, a surgeon who may be required to provide a skin biopsy for the isolation of epithelial cells to make an iPS cell line or an obstetrician or midwife who may be asked to provide an umbilical cord or placenta. This training can be as simple as a one page summary of the regulations for procurement of cells, the importance of donor screening and traceability and the risks of contamination of the tissue or cells being procured and how that it minimised by appropriate practice. It is the responsibility of the DI to assure that procurement is undertaken by suitably trained individuals and a record of all training will need to be retained within the site licence for procurement with the staff named on the training record held by the DI or the holder of the BE licence if that structure is used.

What about reception, storage and dispensing of ATMPs when they arrive from the manufacturer?

All medicines received by a hospital become the responsibility of the chief pharmacist and conventional medicines are stored within the hospital pharmacy until they are dispensed. ATMPs by contrast are often delivered for immediate use with a shelf life measured in hours or, more often, arrive cryopreserved in vapour phase nitrogen. Hospital pharmacies do not usually have capacity for nitrogen storage. Indeed, even if the planned storage is short term within the delivery dry shipper the risk assessments for nitrogen storage and transport of the shipper within the hospital could present a problem since pharmacists are unfamiliar with the risks of vapour phase nitrogen storage. HSCT programmes already have processes and procedures for handling products held in vapour phase nitrogen and for transporting them to the wards for infusion. These will have been established and assessed in accordance with regulatory (HTA) and (where applicable) JACIE standards. Cryopreserved ATMPs are delivered with precise instructions for thawing, together with the associated paperwork to record the process. Haematology staff are familiar with thawing cryopreserved cell suspensions and with completing paperwork associated with these products whereas pharmacists and other healthcare professionals rarely are.

At the Royal Free Hospital the HSCT stem cell laboratory is part of the Centre for Cell, Gene & Tissue Therapeutics (CCGTT). Here, a partnership has been established with the Pharmacy Department such that all cryopreserved ATMPs are received by the HSCT stem cell laboratory staff within the CCGTT rather than through Pharmacy. The products are retained within the cryogenic biobank and dispensed to the clinician when requested. The HSCT stem cell laboratory staff remain responsible for the transport of the ATMP to the patient and the thawing of the product at the patient bedside, irrespective of the clinical team caring for the patient. The HSCT laboratory staff then complete the paperwork and provide copies to the manufacturer and to Pharmacy. The invoice for the service is raised by the CCGTT staff and billed through the Pharmacy business manager.

Ethical considerations

The provision of cells and tissues for therapeutic use requires patient/donor consent. The process of seeking consent may vary in its complexity depending on a number of factors including: the age of the donor; the end use of the tissues and cells and the nature of the product being developed; the number of likely recipients; and for ATMPs in particular, the stage in the development of the product and the likelihood that it will end up in clinical use. Consent forms and information sheets established for an HSCT service are unlikely to be sufficient to cover the manufacture of those cells to an ATMP; tissues and cells procured for these purposes are likely to require their own consent process.

All tissue and cell based therapies are required to undergo some type of a process optimisation and validation, as well as ongoing quality assessment. There are ethical questions related to the use of patient material for these purposes as it is vital to ensure that all donations are put to best possible use; but also are used only for the purposes for which the donor intended. It is common for manufacturers of ATMPs to seek to use excess starting material, or unused products, for internal process development, or long term stability testing. The donor should be made aware of this at the point of donation and their consent sought. The ethical complexity of this process may be increased where a product is being developed by a pharmaceutical company who stand to make a financial gain by placing the final ATMP on the market. Any donation of tissues and cells will provide an invaluable resource. For ATMPs, patient benefit may lie, for example, in the optimisation of the manufacturing process, as well as in the end product. This, however, will not be of direct benefit (financial, or otherwise) to the donor and this should be set out as part of the consent process.

Testing of donors for provision of starting materials for ATMPs is another area which raises ethical considerations that should be covered as part of the consent process. Donors of tissues and cells are required to undergo a panel of mandatory serology tests for markers of infectious diseases. The donated material itself may also be required to undergo testing for certain disease markers, for example as part of product safety testing. The results of these tests may carry implications for the health of the donor and their families. How and when (or indeed whether) the results of any tests will be communicated to the donor should be considered carefully. This will need to be included as part of an informed consent procedure.

Guidance on some of these ethical considerations is provided in the HTA Codes of Practice, and the government advisory committee SaBTO has produced a review of the Donation of Starting Material for Cell-Based Advanced Therapies. As a matter of course, there are some general principles which should be adhered to when seeking consent for the donation of tissues and cells for ATMP manufacture:

<https://www.hta.gov.uk/guidance-professionals/codes-practice/code-practice-1-consent>

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/326823/Cellular_Therapy.pdf

- Any donor should be aware that their donation is given freely, as a gift and is without financial reward. This is in keeping with European Directive 2004/23/EC of the EUTCD which sets out that ' As a matter of principle, tissue and cell application programmes should be founded on the philosophy of voluntary and unpaid donation, anonymity of both donor and recipient, altruism of the donor and solidarity between donor and recipient.'
- The potential future uses of tissue should be clearly explained; donors should be made aware where their tissue could be developed into a commercial product, and where this product could potentially be used to treat many recipients.
- Where applicable, donors should also be made aware of the types of tests the tissue may be subjected to and any possible implications for them and their immediate family member.

Central to all of the above, is that an informed consent process is crucial to protect the safety and well- being of both donor and recipient

Conclusions

ATMPs are the ultimate “patient-specific medicines” and will become mainstream therapeutic options over the next 5 to 10 years. The range of ATMPs already licensed or currently in late phase clinical trials in the US and across the EU is daunting and in 2014 a Japanese group reported the first clinical use of an iPS cell derived therapy [<http://www.dddmag.com/articles/2014/10/japan-starts-world-first-stem-cell-trial-plans-more>] although the trial was subsequently halted due to safety concerns [<https://www.newscientist.com/article/dn27986/>]. It is unlikely that this set back will halt the clinical development of iPS therapies.

The expansion of ATMPs in trials and in routine clinical use will increase the need for expertise in cell and tissue procurement substantially and the handling of cryopreserved cellular medicines in UK hospitals will increase well beyond conventional HSCT services. Meeting these demands will be challenging but UK haematology departments are well placed to serve these needs together with hospital-based virology and microbiology departments who can provide patient/donor screening services for infectious disease markers. Current HSCT units should prepare for the demands this will create by establishing an accurate cost model of their service and by reviewing their procurement quality system to ensure that it is sufficiently flexible to accommodate the breadth of requests likely to be made in the near future and by motivating staff to embrace the challenges ahead.

Table 1 – examples of current ATMPs requiring hospital supply of cell/tissue starting materials

Product	ATMP type	Starting material	Regulatory status
Holoclar – limbal epithelial cell construct	Combination ATMP: Tissue engineered product plus engineered scaffold	Limbal biopsy	Licensed medicine
ChondroCelect	Tissue engineered product	Autologous chondrocytes	Licensed medicine
Mesenchymal stromal cells for immunomodulation	Somatic cell therapy	Bone marrow aspirate	Investigational or unlicensed medicine
Mesenchymal stromal cells for tissue regeneration	Tissue engineered product	Bone marrow aspirate	Investigational or unlicensed medicine
Dendritic cell vaccines	Somatic cell therapy	Autologous peripheral blood monocytes from apheresate	Investigational or unlicensed medicine
TCR-modified T cells	Gene therapy product (GM autologous somatic cells)	Autologous apheresate	Investigational medicine
CAR-T cell	Gene therapy product (GM autologous somatic cells)	Autologous apheresate	Investigational medicine
Activated NK cells	Somatic cell therapy	Autologous apheresate	Investigational medicine
Regulatory T cells	Somatic cell therapy	Autologous apheresate	Investigational medicine
Tracheal construct	Combination ATMP: Tissue engineered product plus allogeneic human scaffold	Autologous bone marrow aspirate and Tracheal biopsy	Investigational medicine
iPS cells	Gene therapy product (GM autologous somatic cells)	Skin biopsy	Investigational medicine

Table 2 – Some considerations in building a business case

- Licence
 - Cost of use of existing HTA procurement licence or modifying an existing MHRA Blood Establishment licence
 - Is a PPD submission to HTA or a licence amendment to MHRA needed for a novel cell / tissue type?
 - Do new staff (e.g. surgeons) need training in HTA / MHRA compliance?
 - What paperwork is needed to cover SOP and labelling of new starting materials?
 - Are changes needed to your existing database for traceability?
 - Do the new starting materials fall within the “30 day pre-procurement” concession for stem cells or will they need to be tested for infectious disease markers on the day of procurement?
- Staff
 - Time needed by HTA DI, MHRA responsible person and the departmental quality manager to set up each procurement?
 - Additional resources needed in the apheresis unit, the haematology out-patient clinic and the “stem cell lab”?
 - Who will cost the service and raise invoices to be sent to hospital finance for processing?
 - Are there adequate staff in hospital finance to bill users for services provided
- Physical resources
 - Cost of apheresis equipment operation, depreciation, replacement
 - Cost of out-patient appointment for bone marrow aspirate
 - Access to operating theatre time for biopsy retrieval
 - Storage capacity for regulatory compliance paperwork and traceability
 - Is there a process within your Trust to set up and approve contracts for provision to academic and commercial customers?
 - Is there a process within your Trust to return part of the income for the service to your department as “income” or to offset QIPP?

References

- RMEG (2014). Building on our own potential: a UK pathway for regenerative medicine. A report from the Regenerative Medicine Expert Group. December 2014. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/415919/build-on-potential.pdf
- Elliot M, DeCoppi P, Speggorin S, Roebuck D, Butler C, Samuel E, Crowley C, Maclaren C, Cochrane L, Jephson C, Janes S, Beaumont NJ, Cogan T, Hsuan J, Lowdell MW, Birchall M. (2012) Stem-cell based tissue engineered tracheal replacement in a child: case report and twenty month follow-up. *Lancet*; 380:994-1000.
- Chabannon C, Hildebrandt M, Scheduling S, Humpe A, Lowdell M, Slaper-Cortenbach I. (2014) Regulation of advanced therapy medicinal products will affect the practice of haematopoietic SCT in the near future: a perspective from the EBMT cell-processing committee. *Bone Marrow Transplantation*; 50:321-323 DOI: 10.1038/bmt.2014.271