



# Regenerative Medicine: Scientific Advances and Regulatory Framework in Europe

FEAM Forum Workshop - Summary report  
27 November 2019, Palais des Academies, Brussels

## About FEAM, The Federation of European Academies of Medicine ([www.feam.eu](http://www.feam.eu))

FEAM is the European Federation of National Academies of Medicine, Medical Sections of Academies of Sciences, Academies of Pharmacy and Academies of Veterinary Sciences. It brings together under one umbrella 21 National Academies representing thousands among the best scientists in Europe.

FEAM's mission is to promote cooperation between its Academies; to provide a platform to formulate their collective voice on matters concerning human and animal medicine, biomedical research, education, and health with a European dimension; and to extend to the European authorities the advisory role that they exercise in their own countries on these matters.

## About the FEAM European Biomedical Policy Forum

The FEAM European Biomedical Policy Forum provides a platform for discussion on key policy issues for the biomedical community.

The Forum is an initiative from the Federation of European Academies of Medicine (FEAM). It aims to bring together representatives from academia, research charities, industry, European and national trade associations and professional bodies, regulators, public health bodies, and patient and consumers groups. If you would like further information on the FEAM European Biomedical Policy Forum or becoming a partner, please contact [info@feam.eu](mailto:info@feam.eu) or [elisa.corritore@feam.eu](mailto:elisa.corritore@feam.eu)

### **Disclaimer**

Opinions expressed in this report do not necessarily represent the views of all participants at the event, the Federation of European Academies of Medicine (FEAM) and its Member Academies, or the FEAM European Biomedical Policy Forum partners.

### **Acknowledgments**

FEAM warmly thanks the speakers, George Griffin and Jacki Davis for their contribution to the workshop as well as Dr Elisa Corritore for writing this report. FEAM is very grateful to the Belgian Royal Academy of Medicine (ARMB) for hosting the event.

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# Background

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This report summarizes the key points of the FEAM European Biomedical Policy Forum workshop on “Regenerative Medicine: Scientific Advances and Regulatory Framework in Europe”, held in Brussels on 27 November 2019.

Regenerative Medicine is considered a novel frontier of medical research and represents an interdisciplinary field that applies engineering and life science principles to promote regeneration, potentially restoring diseased and injured tissues. Substantially, regenerative medicine comprises three main approaches: cell-based therapy, use of engineered scaffolds and implantation of scaffolds seeded with cells. Since the onset of this field, a number of therapies have received Food and Drug Administration (FDA) approval and are now commercially available. In the last years, many scientific advances have been achieved such as the engineering of sophisticated grafts, bioartificial tissues and technologies for integrating grafts with host vasculature. However, there are still emerging needs and challenges to be faced in a global context related to either economic, political and scientific perspective as well as bioethical implications.

In this context, the aim of this workshop was to provide a comprehensive overview on scientific advances, ongoing clinical trials, regulatory perspective, ethical issues and manufacturing challenges of new drugs and products. Finally, the workshop proposed directions for effective future regenerative medicine therapies.

# Summary

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Regenerative medicine is a broad interdisciplinary field defined by the goal of reconstructing, repairing or replacing missing or damaged tissue to a state as close as possible to its native architecture and function. Over the past 2 decades, there have been tremendous advances in the fields of stem cell biology and bioengineering, offering an increased potential to achieve definitive cures for a wide range of clinical pathologies. Since the onset of this field, a number of therapies have received Food and Drug Administration (FDA) approval and are now commercially available. To date, however, clinical success has been achieved mostly in small cohorts of patients due to challenges related to either economic, ethical and scientific implications in Europe.

The FEAM European Biomedical Policy Forum event on Regenerative Medicine was designed to discuss these challenges and to provide a comprehensive overview on scientific innovation, regulatory framework and ethical issues for new advanced therapy medicinal products (ATMPs) in the field of stem cells and regenerative medicine. The workshop brought together speakers from the European Commission, European Medicines Agency, public health services, science communication, academia and industry that proposed directions to be taken to ensure an effective way forward for future therapies.

The discussion on policy and ethical issues was informed by a series of stem cell clinical case studies extended to immunology, hematology and malignancy, diabetes, and epithelium disorders. The major conclusions from the workshop were:

- The need to ensure and support high quality science and gain public trust in order to help patients and their families to fill in the gap between expectations and reality. The public is vulnerable to unscrupulous providers. One option to inform communication would be to develop a new register, listing trials characterised by appropriate standards of robustness and trustworthiness.
- Time is often needed to implement regulation and to provide input. For this reason, the EU requires support from professional bodies - like FEAM - in order to receive advice for policy and regulation making processes.
- The creation of a robust network across disciplines was mentioned. It is necessary to build infrastructure, a framework and seek for public participation.
- Developing sufficient regulatory expertise in biology is a key element for ensuring the determinants of research quality and for monitoring international developments. Highly recommended is the establishment of a new generation of regulators with strong knowledge in molecular biology and possibly virology. It is fundamental to have a combined specialist knowledge. Training and co-education are needed for this purpose.
- Continuing communication between regulators, scientists, clinicians and patients is vital.

- Member State Health Technology Assessment and reimbursement challenges associated with the high cost of novel therapies and the implications for methods to assess risk-benefit and cost-benefit over the long-term are also issues to be tackled.
- Clarifying the role of the EU Advanced Therapy Medicinal Products Regulation is important to provide the framework for regenerative medicine. The reduction of the complexity of the regulatory system is still a challenge. EU requirements are currently tailored more for pharmaceutical compounds than for ATMPs.
- More investment is required for basic science - with more focus on new technologies - rather than having funds allocated in the final steps of scientific research.
- Divergence between hospital exemption and industry is an additional issue.
- A collaborative approach cross-borders is fundamental.

The general discussion highlighted the opportunities for the EU in recognising the importance of investing in basic science, in quality data generation, in promoting multidisciplinary and multisectoral collaboration to enable innovation and its translation to clinical practice.

The EU academies of science and medicine and their networks also have vitally important continuing roles in bringing together all required disciplines and expertises to share data and perspectives and to clarify issues; to raise public, professional and policy-maker awareness; and to support and inform the European Commission on initiatives that sustain research and innovation in this field, strengthening national programmes and supporting collaboration.

## Report of the event

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### Welcome and introduction

Professor George Griffin – President of FEAM – introduced the first session by welcoming participants of the workshop designed to discuss Regenerative Medicine advances in the context of social needs in Europe. In his introduction, Professor George Griffin briefly expanded on the roles of FEAM in promoting collaboration and capacity of building networks between academies of medicine and, based on their expertise in research and clinical medicine, provide the best advice for public health. The FEAM European Biomedical Policy Forum has been developed as a vehicle for joining like-minded people from different disciplines. The Forum normally organizes 3 to 4 meetings a year. The choice of the topics is defined by the members of the Forum.

The FEAM European Biomedical Forum event on Regenerative Medicine is part of a series, examining particular issues for health care in Europe (most recently on ONE Health and anti-microbial resistance). FEAM is committed to working on mutual interests with other academy networks in Europe. An ongoing working group led by EASAC and FEAM was set up in order to prepare a joint statement - to be addressed to European authorities – that describes benefits and challenges in Regenerative Medicine. This joint statement will be used as a basis for a subsequent discussion on scientific, social aspects and the science-policy interface.

In previewing what became a pervasive theme during subsequent discussion, Professor Griffin highlighted the importance of the Regenerative Medicine as fundamental cell-based therapy - which mainly consists in the transfer of cells into a host human body – and emphasized how the use of stem cells in clinics is a field currently evolving very quickly.

## I. Policy Session & Ethics: EU context

The opening remark on the policy and ethic session was provided by Isidoros Karatzas - Head of the Ethics and Research Integrity Sector at European Commission (EC). Isidoros Karatzas mentioned that the latest publication of Ethics advisor in this area dated back to 2015. Isidoros Karatzas asked the audience, specific questions on how EU should inform researchers seeking funding. It is important at this stage to know how Europe can move from principles to research ethics committees. These are big challenges and at the moment there are not very clear answers. For this reason, Isidoros Karatzas proposed to FEAM to contribute to the discussion by developing an ethics guidance for researchers that can be used by all researchers when they are preparing research proposals at the national and EU level. If FEAM prepares it, the EC will use it both as a reference document and to train young researchers and experts participating in Ethics Review Panels. The training of young researchers to incorporate ethics by design in the preparation of their research protocol and to participate in ethics reviews is another crucial aspect.

Isidoros Karatzas continued - asking the audience – for help in training researchers in that area, to provide experts knowledgeable in the field - both in science and ethics – with the objective of increasing the pool of highly qualified reviewers used in the selection process of EU funded projects. The ethics of organoids is currently the topic of an open call in Horizon 2020.

Following the first opening remarks, Patrick Celis - Head of the Scientific Secretariat of the Committee for Advanced Therapies at the European Medicines Agency (EMA) – joined by audio-conference and introduced the perspective from the Regulatory Authority on the challenges for the approval of new regenerative medicine products to be translated to patients.

Regenerative Medicines have the potential to address areas of great unmet medical needs, in indications that are currently untreatable or where the treatment is unsatisfactory, e.g. monogenic disease. The approval of a medicinal product requires that the developer demonstrates the consistency and the controlled quality of the product, and that the efficacy outweighs the potential risks. This demonstration of the benefit/risk profile is based on controlled clinical trials. The marketing authorisation (regulatory approval) will allow the company to put its product on the market in the EU. However, it is acknowledged that ATMPs are different from e.g. a chemical compound, and the pharmaceutical framework has been adapted to take into account the specificities of these products. In Europe, a specific legislation is in place for ATMPs since end of 2008.

Most of these innovative therapies are being developed by academia or small companies (spin offs of academia) instead of big pharmaceutical companies, which adds another layer of novelty to the situation. Several examples of challenges that might hamper the translation of these innovative therapies from the bench to the clinic can be mentioned:



1. For ATMPs, large clinical trials and evidence from a large number of patients is not to be expected. Many of the ATMPs are developed for rare diseases, where only a limited number of patients can be recruited for the clinical trial. Some ATMPs, especially TEP, require a surgical procedure, limiting also the size of the clinical trials. Moreover, most ATMPs are approved on the basis of small trials, less than 100 patients.  
For ATMPs, single arm trials are often conducted and external historical control data or a fixed threshold is often used for comparison. It is crucial to reduce the level of uncertainty by, firstly, collecting high-quality evidence from each patient treated, and secondly, performing post-authorisation activities.
2. As large randomized controlled trials (RCTs) are not really expected for ATMPs, clinical data obtained in exploratory trials are much more important than for other medicines. The reproducibility of results and consistency of batches is essential and manufacturing challenges are common due to the complexity of ATMPs. Product variability might put in question the results obtained from early clinical trials. Developers need to consider earlier - during the product development - the validity, quality and usefulness of all the data they obtain with their product.
3. Regarding the post-authorisation requirements, all approved ATMPs have post-approval commitments, to provide additional safety and efficacy information, from clinical trials, registries or normal clinical use. Small clinical trials also imply that only the most common side effects will be known pre-authorisation, and for those, risk minimisation measures will be put in place. Thinking early in development on how to identify, control and address side effects and/or confirm efficacy after commercialisation will make it much easier for the regulators to accept some higher levels of uncertainties at time of authorisation.

Each of the EU member states have systems in place to assess the value of new medicines entering the market and to reimburse them. The authorities are different from the regulators approving the medicines, and the criteria for effectiveness assessment are different from those to assess the benefit risk for product approval. ATMPs have some characteristics that make them difficult to fit into the standard scheme. First, they are amongst the most expensive medicines (e.g. Zolgensma GTMP to treat spinal muscular atrophy in children - price tag of over \$2 Million). Second, ATMPs contrary to other medicines, are not just intended to treat a disease but may aim to cure patients with a single administration. The limited amount of data at time of approval, including the uncertainty about long-term results and the possibility of serious side effects later in life further complicate the reimbursement decisions. Innovative payment/reimbursement methods are being considered, such a pay per performance and subscription-based cost.

The role of the EMA is limited, but legislative proposal on health technology assessment is under discussion at the European Parliament. Efforts are made to align the information needed for marketing authorisations and patient access: the clinical trial design should be suitable for both purposes. Health Technology assessment bodies can, on request of the developer, be involved in EMA scientific advice on the clinical development programme.

Patrick Celis concluded that the EU regulatory framework ensures the high quality, efficacy and safety of advanced therapy medicinal products in gaining access to the EU market, and that appropriate post-authorisation activities are in place to safeguard public health. ATMPs are a special kind of medicines that forces the authorities to apply more flexibility for their requirements, and to rely more on post-



approval data generation. Early interaction with regulators is recommended not only on manufacturing issues, but on the entire clinical development programme. As ATMPs often hold an enormous therapeutic potential and address diseases where there is a clear unmet medical need, priority and accelerated schemes are being set up within the regulatory systems. The EU: PRIME scheme will further facilitate the early interactions with the regulatory bodies. The downstream processes (reimbursement) are the next hurdle to tackle to ensure that these innovative products reach patients who need them.

The third panelist speaker of the policy and ethic session was Sile Lane - Head of International Campaigns and Policy at Sense about Science. Sile introduced her presentation by describing the work that Sense about Science follows with researchers and researcher organization to help on communication by providing an overview of the public perspective. Sense about Science have 17 years of experience in working with people - affected by chronic conditions - with their family and research charities. Those patients are often exposed to the illusion of miracle cures that are often unreliable. The Lancet Commission has prepared few years ago a document highlighting the gaps between people expectations and reality [Cossu et al. 2017]. Patients are often vulnerable and there are growing concerns on clinical trials in the Regenerative Medicine field. Trials appear to be legitimised by being registered normally on databases and unscrupulous operators are often asking patients to consent for unproved and unlicensed products. Sense about Science agreed with the recommendation from the Lancet Commission paper, which is seeking for standards on robustness and for good clinical trials. Sile Lane also mentioned that her institution aims to collect feedback from patients and many of them look for information and more specific indications about new potential therapies.

Following Sile Lane's opening remark, Giulio Cossu - Professor at the Division of Cell Matrix Biology & Regenerative Medicine at the Manchester University - joined the session by emphasizing the concept that Isidoros Karatzas initially highlighted, regarding the ethical issues in Regenerative Medicine on the use of stem cells. The costs for such therapies are in fact very high. Giulio Cossu stated that a significant number of companies are relying on clinical trials with modest results but still charging high price. Most of these products might be in fact used as treatment but not as a cure, they may delay the problem, but the costs are still very high. A company can survive only if its product is successful. Another issue has been mentioned to be patient's eligibility and clinical criteria necessary to choose the patients. As previously mentioned by Patrick Celis, continuity of interaction between clinical researchers and regulators is very important. There are still aspects that must be optimized. Stem cell clinics are becoming more and more sophisticated while clinicians write protocols that lead to modest results but still published in leading journals. "Do patients pay?" is a key criterion in distinguishing between a fully legitimate trial and one that is premature/quasi-marketing.

During the panel discussion, several aspects have been emphasized:

Different opinions come from the different member states, but a crucial point is the time that EU has to prepare policy and to stimulate discussions. Time is very important. We need time for regulation and time to provide input. For good science you also need time, but patients do not have time, and this is a difficult position. When scientists plan to start a trial, they in fact don't know what are going to be the results.

Trust is also very important. Patients often ask themselves "Can I trust researchers?". It is important to be open, honest, pro-active to gain trust. Engagement with regulators as fast as possible is also very important, as well as preparing patients on what they are going to do, on the costs around it, on the status of the research, to be aware of both benefits and risks. Public and patients are vulnerable, the

gap between expectations and reality has to be filled, otherwise we risk disappointment and loss of license because people are less willing to volunteer. We must rationalize this gap.

Isidoros Karatzas's comment also highlighted the importance to enable researchers to do the work, while asking both researchers and clinicians to be proactive in ethics. If we want to support innovation, we need to support researchers by also providing easy access to the compliance and legal persons in charge. We need a network across disciplines. We must build a structure and a framework and seek public participation in preparing ethics guidelines. The training of researchers in this area is crucial.

The Lancet commission paper was mentioned since this document highlighted challenges on Regenerative Medicine based on lack of robust science-based evidence, poor clinical study design, poor and inconsistent reporting. On this Giulio Cossu intervened saying that sometimes the poor clinical design is the result of a very limited patient group population tested, associated with the huge phenotypical variation among the population that is often encountered. In addition to this, a company can't say "it didn't work", companies would rather say that there is a small effect that has to be improved. The specification of the chemical composition of a cell can't be asked by the regulators, as this is simply impossible to know at the level of each single molecule. Regulators often don't have the cultural background to evaluate this novel level of complexity, therefore a new generation of regulators with strong knowledge in molecular biology and possibly virology is needed.

During the interactive panel discussion with the audience, additional aspects re-emerged such as the need for improving communication between regulators, scientists, patients and the reimbursement of costs for clinical research. George Griffin commented saying that risk is also very important to be evaluated. Patients can decide if they wish to have a treatment once they know the risks. These risks must be clearly explained. But often, we don't know which the risks are at the very beginning. An additional comment from the audience also raised the issue on the complexity of the informed consent process.

Increasing competition for commercialization of regenerative medicine products from outside Europe brings new challenges. Some are concerned that the EU is falling behind and there is agreement that regulatory frameworks should aim to enable rather than hamper. The EU should respond to international competition by emphasizing its attention to ethics and research integrity, its quality of protocols and research procedures, and must continue to critically monitor developments.

To conclude the session, the moderator asked each speaker to mention the top priorities and the urgent needs currently necessary to move forward in the field:

Giulio Cossu: The need for evaluating ethical aspects and supporting innovation, regulation and patient involvement. All are aspects that must be addressed at the same time. EU funds can pay just for Phase 1 clinical trials. Therefore, this is a barrier for universities that can't to move further.

Sile Lane: Communication must be improved, more clarity in explaining challenges is requested.

Isidoros Karatzas: Need of the support of professional organizations - like FEAM - in order to advise on policy and (if needed or necessary) regulation processes. The EU needs this input from the experts.

## II. Scientific Session: Research and Innovation

The second scientific session began with the presentation of Johan Hyllner - Senior Director and Head of Regeneration at AstraZeneca and Professor at the Linköping University. Johan Hyllner explained that cell therapy started with the first blood transfusion and bone marrow transplantation in the 1960s. In this field, there are currently 7 technology areas:

- Ex vivo gene modification with viral vectors (CAR-T ex)
- Somatic cells or mesenchymal stem cells
- In vivo gene modification with viral vectors
- 3D technology (decellularized organs, scaffold)
- Cell immortalisation
- Genome editing
- Cell plasticity (change the phenotype with iPSCs and embryonic stem cells)

These new technologies can be applied for a wide range of diseases such as diabetes, cancer and represents a potential reality. Different cell sources can be used for these treatments: somatic cells, pluripotent stem cells, immune cells, gene modified cells. There are at the moment about 1000 cell-based clinical trials ongoing globally. Among these, about 100 are in phase III with 50 % ongoing in the field of oncology and 10 % in the cardiovascular disease area.

Some of AstraZeneca's and Johan's current work is focused on the generation of beating cardiac ventricular cells produced by ESCs as potential treatment for myocardial infarction and heart failure. The differentiation protocol foreseen 6 days, followed by cell purification and intramyocardial injection. Cell therapy's benefits are well known however, there are still challenges to face, which include also business-related issues, reimbursement procedures, manufacturing supply chain hurdles, robustness of the process, scale-up. In addition, scientifically there are still issues concerning the chemistry manufacturing control (CMC), the route of delivery, gene introduction. The clinical and regulatory challenges include the nature of the preclinical package (e.g. disease models used), trial design and issues for clinical adoption. To date, various ATMPs have been granted with marketing authorisation but fewer managed to secure reimbursement. There is now a national centre – called Centre for Advanced Medical Products - focusing on challenges in ATMPs. This centre is composed by 29 partners representing academia, industry and healthcare. Regulatory challenges, for academies and small companies represent still a relevant issue. From an EU perspective, collaboration between different nations is a strength and collaboration is the way to move forward.

The second panellist speaker of the Scientific session was introduced by Prof Stefan Constantinescu – FEAM Vice President. James Griffin is Consultant Haematologist at the University Hospitals Bristol and NHS Blood & Transplant. His work was mainly focused in understanding the massive interaction between immune system and cancer. Specifically, hematopoietic stem cell transplantation requires a donor - from who cells are harvested – and a recipient who needs disease eradication. The allograft activity in Europe is increasing since the 1998. Transplantations are mostly required for indications such as myeloid malignancies, lymphoid malignancies, solid tumour and non-malignant diseases. In the last decades, the survival probability in patients significantly increased and three study cases were mentioned by James Griffin. The causes of death post-transplant might be due to primary disease, graft-versus-host disease (GVHD), infections, organ failure, second malignancy and others.

In stem cell transplantation, different choices of conditioning can be applied (full intensity vs reduced intensity, T-replete or T-deplete, GvHD prophylaxis, bone marrow vs peripheral blood stem cells). In the future, increasing use of CAR-T may change transplant habits. A patient diagnosed with acute lymphoblastic leukemia was treated with allogeneic transplant of CAR-T cells. After a relapse 5 months following the transplant, the patient experienced remission of the disease. The trial therapy used for him it has now 89% of success rate for patients. In this new cell therapy field, it is necessary to have proper investment on logistics, GMP and storage facilities for advanced therapies. Stem cell transplantation has the ability to cure patients from malignancy although the concept is highly complex and risky. But newer cellular therapies hold great promise for refractory and relapsed diseases.

The session continued with the presentation of Lorenzo Piemonti – Professor at the Hospital San Raffaele of Milan and chief of the Diabetes Research Institute – that provided an overview of the application of Regenerative Medicine in the field of Type 1 Diabetes (T1D). This disease is considered to represent a perfect clinical model to test a cell replacement therapy because pancreatic cells produce circulating hormones, so that cells need not be transplanted into their original site. There are at the moment well defined clinical outcome to measure the tissue function, in the specific the C-peptide secretion that provided a proof of principle with islet transplantation (IT). If we look at the comparative efficiency of the IT versus the whole pancreas transplantation, about 70% of patients with islets transplant showed successful engraftment 5 years later with the longest graft survival measured at 15 years compared to the 23 years showed by the whole pancreatic organ transplant. These numbers give a vision on the long-term effects and efficacy of cell transplantation. About 20 years ago, the insulin independence was reached only up to 2 weeks from the transplant, clearly showing the massive improvement in this field over the last decades.

Diabetes is regarded as a chronic disease, but patients with T1D have 12 years less life expectancy versus the 3-8 years showed by patients affected by breast cancer compared to health individuals. The success reached nowadays in this field is explained by the implementation of new tools and improved knowledge on:

- Protocol for making pancreatic progenitors or beta cells from human pluripotent stem cells. These results have been published from many groups in the world and are reproducible
- Evidence for the reversion of the cycle of the developmental potency. Before we believed that somatic cells couldn't revert their phenotype to a pluripotent state. But thanks to Shinya Yamanaka and his discovery on four specific transcription factors, we can now generate new pluripotent stem cells in vitro starting from somatic cells. The field is moving
- Immuno-isolation devices such as the Encaptra drug delivery system

Lorenzo Piemonti is currently involved in three different clinical trials in phase 3, thanks to the Horizon 2020 consortium that includes partners from Brussels (UZ Brussel and VUB), San Diego (ViaCyte), Milan (San Raffaele Hospital Diabetes Research Institute), Lausanne (Nestlé Institute of Health Sciences), Leiden (the University Medical Center) and Paris (Institut du Cerveau et de la Moelle Epinière. We are now moving from personalized treatments to personalized cure in diabetes by having at disposal good embryonic stem cells (ESCs), good differentiation protocols and immuno-protection tools.

These new generation of cells, produced by using differentiation protocols designed in order to recapitulate the whole structure of the human pancreatic islets, are capable to secrete insulin, glucagon, somatostatin and to respond to glucose challenges. To move this technology to the patients, we need scaffold for the cells (or decellularized organs). The organ decellularization strips cells out and preserve the natural organ architecture. However, the engraftment for the cells is still one of the major issues: about 70% of islets are normally lost within the 1<sup>o</sup> week after transplantation because of lack of engraftment and vascularization.

Gene editing and the CRISPR technology are currently used - for in vitro testing - to generate cells “invisible” to the immune system, for example by depleting HLA class I molecules or the B-2 macroglobulin or by inserting HLA-E to avoid recognition from CD8+ and natural killer cells.

The last speaker of the scientific session was Graziella Pellegrini – Professor at the University of Modena and Reggio Emilia (Center Regenerative Medicine). Graziella Pellegrini during her presentation shared her professional experience on the field of regenerative medicine.

The first attempt in this field is dated back to with the isolation, manipulation and transplantation of cells in vitro. Graziella’s experience started in the ‘80s with the work on epithelial cell transplantation used to treat at first large skin lesions of III<sup>o</sup> degree burns (about 80-90% burns on the body surface). Franco was the first patient treated and he is now conducting a normal life. Since then, hundreds of patients were treated with epithelial cell transplant also outside Italy by reducing superficial scars and avoiding the wheelchair for those patients.

The application of this technique was then expanded to additional organ diseases. Protocols were optimized by manipulating melanocytes and keratinocytes used in co-culture to treat vitiligo and piebaldism. Another stream of work also included the treatment for the hypospadias, in which children are born without urethra in the penis. The reconstruction of the urethra was obtained starting from a very small biopsy. The tubulization was re-created in vitro and today – after 10 years from the transplant – the 15 patients treated are fine and in continue follow-up.

The epithelial cell transplantation also led to successful results as cure for blindness due to corneal epithelial limbal cells deficiency. The corneal epithelial culture containing stem cells was transplanted in patients that re-acquired partially or globally the vision. This treatment is still effective 20 years later. These patients are today in continue follow-up and recovered the corneal integrity.

Additional work was then conducted by using gene therapy in the context of Epidermolysis bullosa, a disease characterized by the loss-of function of adhesion molecule between epithelial and connecting tissues. Claudio was the first patient transplanted with engineered corrected cells obtained from the skin of his legs. The autologous stem cells were modified by using a retroviral vector. Once the corrected skin was obtained in vitro, cells were transplanted on his legs, restoring the normal skin surface. Since the 2005 - year of the transplant – the skin is still in perfect conditions, however, it wasn’t possible to fully cure this patient because on 2007 a new regulation came, tailored for chemical compounds and not for ATMPs.

Since the 2007, Graziella’s team has received approval just for two products, including the one for tissue engineering in ocular surface, recognized as the first stem cell-based product approved in Europe. The second one was the product based on the gene therapy modification of skin cells for the treatment of epidermolysis bullosa (currently in phase I and II). It was very famous the case of a Syrian child in intensive care with 80% of loss skin surface. From small biopsies, stem cells were isolated and used to

induce a full recovery of the body skin. This is the proof that regenerative medicine can represent a definitive cure and can change completely the life of patients.

However, a very limited amount of products are currently distributed in Europe, because of reimbursement problems for example. If we have a very limited number of products, we have a problem. Europe has big experience and knowledge in research that produced public skepticism. Why this problem? The complexity of the system. It is fundamental to have a combined specialist knowledge because there are no specialists available at the moment. Moreover, we assist to a strong increase in costs due to the resetting of the technology because scientists must undergo regulatory revision and rebuild the entire process every time, wasting money. EU requirements are tailored more for pharmaceutical compounds than for ATMPs. The industry is not in the field of ATMPs. In Europe there is a lot of competition between hospital exemption models and industry which unpairs the sustainability of this very promising field.

The scientific process starts with the basic science, we identify the medical need and the patients, based on regulatory rules. Then we proceed with clinical translation and the definition of clinical protocols based on the analysis of preclinical models. Following this path, we have then the evaluation of the follow-up and the collection of all end points.

In all this process an improved understanding of the biological mechanism is needed. At the very beginning of this process we are not aware of the full biological mechanism. More investment is required for basic science as well as the need of having biology and regulatory knowledge, together, associated. We need people understanding both fields and co-education and expertise from biologists and regulators. The training of experts, the reduction of the complexity of the system in Europe and the divergence between hospital exemption and industry are key issues to be faced. The problem is not the shortage of the funding but the waste of them.

More funds for basic research are requested behind diseases with more focus on new technologies rather than focusing in final steps of a scientific research. A collaborative approach cross-borders is fundamental. Funds for GMP align must be available also for academies. The panel discussion finally re-emphasized the importance of having a category of experts in regenerative medicine, facilitating the harmonization between different parts of work and reducing costs of production for new technologies.

### III. Closing remarks

Professor George Griffin closed the session by emphasizing the pace of advance. Many years ago, the name 'stem cells' didn't even come through. Imaging, ultrasound, CT, radiotherapy scans were developed during his medical school. But now, the scientific world is speaking about stem cells and organoids as tools to treat human diseases. We are just at the beginning and we will learn more but the link between basic and clinical science is obvious. They are not different. They must be intertwined.



# Annex I – Table of key statements

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Table containing the key statements suggested during the workshop:

Presenter	Key Statements
Isidoros Karatzas	<ul style="list-style-type: none"> <li>- Time is needed to implement regulation and to provide input. EU requires support from professional bodies in order to receive advice for policy and regulation making processes.</li> <li>- Ethics guidance is needed for researchers for the preparation of scientific proposals at the national and EU level. This guidance would increase the pool of highly qualified reviewers used in the selection process of EU funded projects.</li> <li>- The creation of a robust network across disciplines was suggested. It is necessary to build infrastructure, a framework and seek for public participation.</li> </ul>
Patrick Celis	<ul style="list-style-type: none"> <li>- ATMPs force the authorities to apply more flexibility for their requirements and to rely more on post-approval data generation.</li> <li>- Early interaction of researchers with regulators is recommended not only on manufacturing issues, but on the entire clinical development programme. The EU: PRIME scheme will further facilitate the early interactions with the regulatory bodies.</li> <li>- The downstream processes (reimbursement) are the next hurdle to tackle to ensure that innovative products reach patients who need them.</li> </ul>
Sile Lane	<ul style="list-style-type: none"> <li>- To ensure and support high quality science and gain public trust is needed in order to help patients and their families to fill in the gap between expectations and reality. The public is vulnerable to unscrupulous providers.</li> <li>- A possible way to improve the inform communication for patients would be the development of a new register, with listing trials characterised by appropriate standards of robustness and trustworthiness.</li> </ul>
Giulio Cossu	<ul style="list-style-type: none"> <li>- Continuing communication between regulators, scientists, clinicians and patients is vital.</li> <li>- Member State Health Technology Assessment and reimbursement challenges associated with the high cost of novel therapies and the implications for methods to assess risk-benefit and cost-benefit over the long-term are issues to be tackled.</li> <li>- Developing sufficient regulatory expertise in biology is a key element for ensuring the determinants of research quality and for monitoring international developments. Highly recommended is the establishment of a new generation of regulators with strong knowledge in molecular biology and possibly virology. It is fundamental to have a combined specialist knowledge. Training and co-education are needed for this purpose.</li> </ul>
Johan Hyllner	<ul style="list-style-type: none"> <li>- Cell therapy's benefits are well known however, there are still challenges to face, which include business-related issues, reimbursement procedures, manufacturing supply chain hurdles, robustness of the process, scale-up. In addition, there are still issues concerning the chemistry manufacturing control (CMC), the route of delivery, gene introduction. The clinical and regulatory challenges include the nature of the preclinical package (e.g. disease models used), trial design and issues for clinical adoption.</li> <li>- To date, various ATMPs have been granted with marketing authorisation but fewer managed to secure reimbursement.</li> <li>- From an EU perspective, collaboration between different nations is a strength and collaboration is the way to move forward.</li> </ul>



James Griffin

- In this new cell therapy field, it is necessary to have proper investment on logistics, GMP and storage facilities for advanced therapies.
- Stem cell transplantation has the ability to cure patients from malignancy, although the concept is highly complex and risky. But newer cellular therapies hold great promise for refractory and relapsed diseases.

Lorenzo Piemonti

- New generation of cells are produced by using differentiation protocols designed in order to recapitulate the whole structure of the human pancreatic islets.
- However, the engraftment for the cells is still one of the major issues: about 70% of islets are normally lost within the 1<sup>o</sup> week after transplantation because of lack of engraftment and vascularization.

Graziella Pellegrini

- Clarifying the role of the EU Advanced Therapy Medicinal Products Regulation is important to provide the framework for regenerative medicine. The reduction of the complexity of the regulatory system is still a challenge. EU requirements are currently tailored more for pharmaceutical compounds than for ATMPs.
- More investment is required for basic science, with more focus on new technologies, rather than having funds allocated in the final steps of scientific research.
- Divergence between hospital exemption and industry is an additional issue.
- A collaborative approach cross-borders is fundamental.

# Annex II - Agenda



## Workshop

### *“Regenerative Medicine: Scientific Advances and Regulatory Framework in Europe”*

27 November 2019 (13:30 - 18:30)

Palace of the Academies, Rue Ducale 1, 1000 Brussels

#### Agenda

Moderator: Jacki Davis, Journalist

13:30-14:00	<u>Registration</u>
14:00 -14:15	<u>Welcome &amp; Introduction</u> George Griffin, President, Federation of European Academies of Medicine (FEAM)
<b>I. Policy Session &amp; Ethics: EU context</b>	
	<u>Opening remarks</u>
14:15-14:20	Isidoros Karatzas, Head of the Ethics and Research Integrity Sector (European Commission)
14:20-14:25	Patrick Celis, Committee for Advanced Therapies (European Medicines Agency)
14:25-14:30	Sile Lane, Head of International Campaigns and Policy (Sense about Science)
14:30-14:35	Giulio Cossu, University of Manchester, Division of Cell Matrix Biology & Regenerative Medicine
14:35 – 15:45	Panel Discussion
15:45-16:05	<u>Coffee break</u>
<b>II. Scientific Session: Research and Innovation</b>	
	<u>Presentations</u>
16:05-16:20	Johan Hyllner, Senior Director AstraZeneca (Head of Regeneration), Linköping University
16:20-16:35	James Griffin, Consultant Haematologist, University Hospitals Bristol NHS Trust NHS Blood & Transplant
16:35-16:50	Lorenzo Piemonti, Hospital San Raffaele, Diabetes Research Institute
16:50-17:05	Graziella Pellegrini, University of Modena and Reggio Emilia - Center Regenerative Med.
17:05-17:35	Panel Discussion
	<u>Concluding remarks</u>
17:35-17:45	George Griffin, President, Federation of European Academies of Medicine (FEAM)
17:45-18:30	<u>Networking cocktail</u>

## Annex III - Speakers' biographies

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### Jacki Davis

*Moderator, Journalist*



Jacki Davis is an experienced journalist, speaker and moderator of high-level events both in Brussels and in EU national capitals, the editor of many publications, a regular broadcaster on television and radio news programmes, and a Senior Adviser and member of the Governing Board of the European Policy Centre think tank. Jacki has been based in Brussels for 25 years, and was previously Communications Director of the European Policy Centre think tank; Editor-in-Chief of E!Sharp magazine; and launch editor of European Voice, the Brussels-based weekly newspaper then owned by The Economist (now Politico). Jacki has moderated many conferences in Brussels and in EU Member States, and also has extensive experience in planning events.

### George Griffin

*President, Federation of European Academies of Medicine (FEAM)*



Prof. George Griffin is Emeritus Professor of Infectious Diseases and Medicine at St George's, University of London, a Board Member of Public Health England and a fellow of the UK Academy of Medical Sciences. Prof. Griffin gained his BSc in Pharmacology and Molecular Biology at King's College London Sciences, where he was awarded the Delegacy Prize for Excellence in Preclinical Science. He was awarded a PhD in Cell Biology/Biochemistry at the University of Hull, and returned to clinical studies at St George, University of London, where he was awarded the MBBS. During this time, he was awarded a Harkness Fellowship of the Commonwealth Fund of New York at Harvard Medical School. On return to the UK, he continued clinical training at the Royal Postgraduate Medical School where he was tutor in Medicine, and the National Hospital for Nervous Diseases. He then returned to St George's as lecturer, was awarded a Wellcome Trust Senior Lectureship and became consultant physician on the Clinical Infection Unit where he was instrumental in developing an internationally renowned research unit twinned to the Clinical Unit. He held prestigious research fellowships in the University of Michigan and National Institutes of Health. Professor Griffin was awarded the distinction of CBE in 2018 (Commander of the British Empire) for his research and its contribution to Public Health. His research has focused on the host response to infection at cell, molecular and whole body level and his principal clinical contributions have been in the characterisation of intestinal disease in HIV infection, mechanisms of weight loss in HIV and definition of loss of mucosal immune response in advanced HIV infection.

## I. Policy Session & Ethics: EU context

### Isidoros Karatzas

*Head of the Research Ethics and Integrity Sector at DG Research Innovation (European Commission)*



Isidoros karatzas is a biochemist by training. He has been a Marie-Curie Science fellow. After joining the European Commission, he was responsible for the ex-post evaluation of the Framework Programme. Consequently, he was a member of the first unit tasked with developing and supporting the scientific advice process. In this unit, Isidoros managed the risk governance research file and was the scientific secretary of the European Research Advisory Board (EURAB), the high-level body advising the Commission on research policy and research priorities. Currently, he is the head of the Research Ethics and Integrity Sector in DG Research and Innovation. As head of the sector, he established advanced training courses on research ethics for Commission staff and the ethics research community and has set up the first European system on ethics checks and follow-up. In addition, the sector oversees the research integrity policy activities, including the relations with relevant stakeholders such as ALLEA, LERU, Science Europe and the business community.

### Patrick Celis

*Head of the Scientific Secretariat of the Committee for Advanced Therapies (European Medicines Agency)*



Patrick Celis joined the European Medicines Agency (EMA) in 1997. He holds a degree in Pharmacy and a PhD in Pharmaceutical Sciences from the University of Leuven, Belgium. Since December 2008, P Celis is responsible for the Scientific Secretariat of the Committee for Advanced Therapies (CAT). Before become Head of the CAT Secretariat, P Celis was responsible for the coordination of EU authorisation procedures for biological/biotech products and for the following scientific projects: Pandemic influenza vaccines, TSE, viral safety of recombinant products and Cell-based medicinal products. He held the positions of Scientific Secretary of the Vaccine Working Party and the Cell-based Products Working Party. Since 2006, he was involved in the implementation of the Regulation on Advanced Therapy Medicinal Products at the EMA. Prior to joining the EMA, P. Celis worked for 2 years as Pharmaceutical Assessor at the Belgian Ministry of Health.

## Sile Lane

*Head of International Campaigns and Policy at Sense about Science*



Sile is head of international campaigns and policy, leading our current campaigns which include AllTrials, a global campaign for the registration and reporting of all clinical trials and Ask for Evidence, a public campaign to help people request for themselves the evidence behind news stories, marketing claims and policies. Sile was one of the original founders of the AllTrials campaign, alongside Ben Goldacre, growing it from a simple petition to a high profile, worldwide campaign. In 2016 she gave the keynote speech at TEDxMadrid, "The Hidden side of Clinical Trials". Sile previously worked on the Libel Reform campaign which called for reform of the libel laws to protect open scientific discussion. The groundswell of support for the campaign led to the passing of the Defamation Act 2013 that changed the law in England and Wales. In the policy arena, Sile works closely with our director Tracey, to promote transparency in government processes. She also oversees the organisation's EU office, which calls for EU citizens, researchers and the European parliament to scrutinise and share evidence behind European policymaking. Most recently, Sense about Science organised public-led events in Westminster, the Oireachtas in Dublin and the European parliament, to remind elected officials that evidence matters to the public. A sought-after chair, panellist and engaging public speaker, Sile has appeared on RTÉ and the Today programme, as well as writing for the Guardian among other publications. Sile is passionate about science communication and spends a lot of time helping researchers, regulators, policymakers, companies and NGOs to talk about science and evidence openly, humanly and without stigma and intimidation. She founded the Dublin office of Sense about Science in 2016 and recently launched Voice of Young Science in Ireland, a unique and network of early career researchers committed to playing an active role in public discussions about science. Prior to joining Sense about Science in 2009, Sile was a post-doctoral researcher at Imperial College London working on stem cells and regenerative medicine.

## Giulio Cossu

*Professor of Regenerative Medicine, Division of Cell Matrix Biology & Regenerative Medicine (University of Manchester)*



Giulio Cossu received his MD degree from the University of Rome in 1997. He trained as a Fogarty post-doctoral at the Wistar Institute, University of Pennsylvania (1980-83), and then became Associate Professor at the Dept. of Histology and Medical Embryology of the University of Rome "La Sapienza". In 1991 GC was promoted full Professor and in 1993-4 was a visiting professor at the Pasteur Institute in Paris. In 2000 he was appointed Director of the "Stem Cell Research Institute" of the Hospital San Raffaele in Milan. In 2003 he was appointed as Scientific Coordinator of the newly created San Raffaele Biomedical Science Park of Rome, while maintaining his position in Milan. Since 2005 he is Professor of Histology and Embryology at the University of Milan. In 2008, he was appointed Director of the newly created San Raffaele Division of Regenerative Medicine. In 2012 GC became Professor of Human Stem cell Biology at University College London, and in September 2013 Constance Thornley Professor of Regenerative Medicine at the University of Manchester. Giulio Cossu is recognized for his pioneering work on skeletal myogenesis and for the first cell therapy trial with stem cells for muscular dystrophy. He also pioneered studies on myogenic cell heterogeneity by showing intrinsic differences among embryonic, foetal and adult myogenic progenitors. Overall, Giulio's research activity is characterized by the unique ability to combine work in developmental biology with cell therapy, successfully translating results obtained in mammalian embryos into clinical protocols in patients.

## II. Scientific Session: Research and Innovation

### Johan Hyllner

*Senior Director AstraZeneca (Head of Regeneration), Prof at the Linköping University*



Johan Hyllner is the Head of Regeneration of early CVRM, BioPharmaceuticals R&D at AstraZeneca. Johan is also Professor in Engineering Biology at the Department of Physics, Chemistry and Biology at Linköping University in Sweden and has published more than 60 peer reviewed, full-length articles. Prior to joining AstraZeneca, he was the chief scientific officer of the Cell and Gene Therapy Catapult, London, UK. Johan has held a range of senior management roles in the European and US cell therapy industry. In addition to Catapult, Johan has worked at Cellectis, Cellartis, Vitrolife and Hoffmann-La Roche. He has a broad expertise ranging from applied research through development, global marketing, manufacturing and commercialization of cell and gene technology-based products. Furthermore, Johan has been responsible for external scientific relations, assessment of projects and technical oversight of preclinical programs. He has extensive transaction experience and has been involved in major collaborative projects with industry and academia.

### James Griffin

*Consultant Haematologist, University Hospitals Bristol NHS Trust - NHS Blood & Transplant*



Dr Griffin is a specialist in Therapeutic Apheresis and Cellular Therapy. He is the Clinical Director Therapeutics at NHS Blood & Transplant responsible for a national network of Apheresis units, Stem Cell and Immunotherapy Laboratories, a Clinical Biotechnology Unit, two Advanced Therapies GMP facilities, the British Bone Marrow Registry, the UK Cord Blood Bank and UK Tissue procurement and delivery. Working as part of the team at University Hospitals Bristol NHS Foundation Trust, he specialises in myeloma, stem cell transplantation and immune effector cell therapy. Dr Griffin completed his PhD in Adoptive Immunotherapy at UCL which highlights his longstanding interest in the immune system and the clinical application of cellular therapy.



## Lorenzo Piemonti

*Hospital San Raffaele, Diabetes Research Institute*



Lorenzo Piemonti, MD, born in Carate Brianza, graduated with Summa cum Laude at the University of Milan in 1994, and specialized with Summa Cum Laude in Endocrinology and Metabolic Diseases and in Micro and Experimental surgery at the University of Milan in 2000 and 2004, respectively. At the San Raffaele Scientific Institute (Milan, Italy), he serves as Director of Diabetes Research Institute, Director of Human Islet Transplantation Program ([http://www.sanraffaele.org/ENGhome/research/divisions\\_centers\\_institutes\\_research\\_programs/ITP/index.html](http://www.sanraffaele.org/ENGhome/research/divisions_centers_institutes_research_programs/ITP/index.html)). He also serves as Chief of the Beta Cell Biology Unit (Diabetes Research Institute), and Director of Human Islet Processing Facility, and coordinator of European Consortium for Islet Transplantation that has been providing Human beta Cell Products for research and clinical applications at OSR, in Italy and across state barriers in Europe since 2000 (See European Consortium for Islet Transplantation, <http://ecit.drisanraffaele.org/en/islet-transplatntation/index.html>). He also serve as Professor in Endocrinology at University "Vita Salute San Raffaele" of Milan and as Honorary Visiting Professor at Vrije Universiteit of Brussel. His area of expertise is mainly focused on diabetes and pancreatology. In particular, he has large experience about diabetes and pancreatic cancer. He has in the past studied the role of innate immunity in islet cell biology (especially in the human model of islet transplantation in type 1 diabetes recipient) and in pancreatic cancer biology (especially the role of chemokines and chemokine receptor system in inducing leukocytes infiltration). In addition, his research interests include beta cell replacement, immune tolerance induction strategies, dendritic cell biology, and stem cells. He currently serve as section Editor of Cell Transplantation-the Regenerative Medicine Journal and of Current Diabetes Reports, as editorial board of Acta Dabetologia, as Councilor of the International Pancreas and Islet Transplantation Association (IPITA) of The Transplantation Society (TTS), as member of the National Committee for Food Safety (2018-2021, Italian Ministry of Health) and previously (2011-2017) as member of the European Pancreas and Islet Transplantation Association (EPITA) committee of European Society for Organ Transplantation (ESOT).

## Graziella Pellegrini

*University of Modena and Reggio Emilia, Center Regenerative Med*



Graziella Pellegrini is Full Professor at the University of Modena and Reggio Emilia and Cell Therapy Program Coordinator at the Centre for Regenerative Medicine "Stefano Ferrari". She is also co-founder and R&D Director at Holostem Terapie Avanzate S.r.l. She graduated in Chemistry and Pharmaceutical Technologies (1988) and in Pharmacy (1889) at the University of Genova. She coordinated scientific teams in laboratories in different cities. Prof. Pellegrini is founding member of the International Ocular Surface Society and member of major scientific societies and international committees. She was awarded for a research on central nervous system, for research on ocular pathology and for research on urethra and received the ISSCR Award of Innovation in 2018 (with Michele De Luca). Author of 9 patents, 9 book chapters and over 70 peer reviewed publications in the major international journals, she was invited speaker or chairman in approximately 230 major international meetings on Stem Cells and Regenerative Medicine. Prof. Pellegrini is one of the two inventors of the technology for culture and transplantation of limbal stem cells for treatment of blindness due to corneal stem cell deficiency and collaborated to the orphan drug designation and European registration of the therapy. She developed other translational medicine protocols for treatment of third-degree burns, depigmentation and is collaborating to a phase I clinical trial on gene therapy of epidermolysis bullosa. She is currently working with her team, on oral mucosa, urethra and airway epithelium.





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