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Short Report

A discussion on cell therapy in Manchester

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1. An EMBO conference on cell therapy and its clinical applications

It might come as a surprise to many, that stem cell transplantation is actually an established, life saving therapy for certain diseases affecting the haematological system and stratified epithelia. This is made possible by the chemical (chemotherapy) or physical (radiation) ablation of the affected bone marrow or surgical removal of diseased epithelia. The elimination of affected tissues thus makes "room" for donor cells, which consequently engraft with high yields, effectively replacing the diseased tissue with a healthy one.

This is, at the state of the art, clearly an impossible task for most tissues such as the brain and cardiac or skeletal muscles. Furthermore, intrinsic structural and functional differences among different tissues affect transplantation outcome. Finally and just as important, long-term stem cell self-renewal differs dramatically among different tissues, significantly impacting on the long-term regeneration potential of each tissue. It is mostly for these reasons that attempts to treat degenerative diseases of other tissues such as brain or heart with cell therapy, have so far met with generally modest results at best.

In the last twenty years, gene therapy has moved, not without considerable problems, into the clinical arena, and cell-mediated gene therapy especially has produced encouraging, and in some case striking results, again for genetic diseases of blood and epithelia.

Hundreds of clinical trials have started, are running or have been completed for diseases of different tissues. While many remain unpublished, the results of some are becoming available, together with valuable experience gained from both successful and unsuccessful trials. This information will be of critical importance to refine protocols and implement tools aimed at achieving clinical efficacy. Unfortunately, however, many poorly controlled trials are also taking place and will inevitably bring confusion to a growing field; poorly controlled trials will also raise unjustified expectations in desperate patients and/or their parents who cannot evaluate the soundness of trials that they learn about through the social media.

For all of these reasons, we felt that a conference specifically focused on the clinical translation of stem cell-based research, on running trials and their follow-up and their impact on society, was sorely needed to offer a timely picture of such a rapidly evolving and partly controversial field.

2. The topics

Given the broad and sometimes ill-defined distinctions among the various disciplines, we decided to focus on both allogeneic and autologous genetically corrected cell therapy, with the exclusion of "in vivo" gene therapy (Fig. 1), and cancer or basic stem cell biology, all huge areas in their own right and covered in many other excellent meetings. The conference was funded by the EMBO Courses and Workshops Programme and co-sponsored by the University of Manchester, with contributions from e-Life, Holostem Terapie Avanzate and the patient associations, "Duchenne Parent Project — Italy" and ReACT.

3. What is working or promises to?

Each session was dedicated to diseases predominantly affecting a tissue/organ, namely the haematopoietic system, epithelia, skeletal and cardiac muscle, brain and bone, with a keynote lecture by Kathryn Wood (Oxford University), dedicated to the immunological hurdles in cell transplantation and describing the underlying mechanisms together with strategies that might be implemented to overcome undesirable

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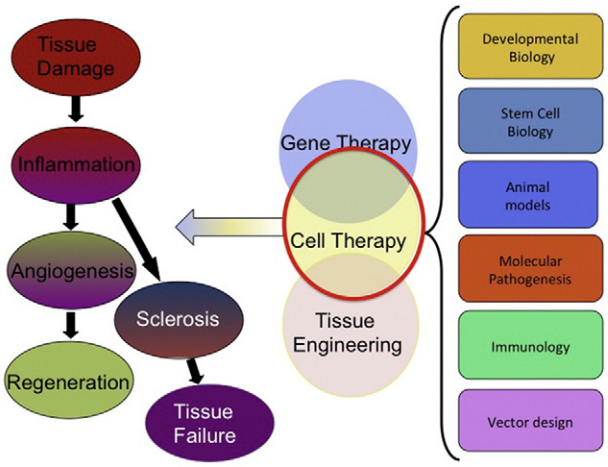

Fig. 1. An over-simplified scheme of gene therapy, cell therapy and tissue engineering, also showing the basic science and technology that feeds into these disciplines. The scheme also shows the stage of the pathological process where new therapies should promote regeneration and prevent fibrosis and tissue failure.

immune responses (Wood et al., 2016). A special session was dedicated to the ethical and regulatory issues arising from this new and rapidly evolving area of medicine.

Below, we will mention a few examples of the exciting new results presented at the meeting, keeping in mind that the long-term follow-up of a cell-based therapy is equally important, albeit less exciting and "glamorous" than a report on a new successful outcome of cell therapy for a disease. We apologize to those speakers who we could not quote due to space constraints (the complete list of speakers is available at: http://events.embo.org/15-cell-therapy).

The Conference was opened by a keynote lecture by Luigi Naldini (TIGET, San Raffaele), who gave an overview of the current state of ex-vivo gene/cell therapy and provided an update on the on-going metachromatic leukodystrophy trial (Biffi et al., 2013), the follow up of the first successfully treated patients, as well as on the new gene transfer tools that may soon enter the clinical arena.

In the haematological diseases session, several leaders in the field reported on the state of the art of the on-going or pending trials for the treatment of Wiskott–Aldrich syndrome (Alessandro Aiuti, TIGET, Milan), SCID, haemoglobinopathies (Marina Cavazzano, Necker, Paris) and Fanconi anaemia (Jaun Bueren, CIEMAT, Madrid). Clearly, each one of these diseases poses different biological and clinical problems (reviewed in Cicalese and Aiuti, 2015; Cavazzana et al., 2016). The approach undertaken, though tailored for each specific disease, is, nevertheless always based on auto-transplantation of gene corrected autologous haematopoietic stem cells (HSCs). The results appear quite promising and the coming years will inform us on efficacy, as in the case of ADA deficiency, now celebrating the fifteenth year of follow up of the first treated patient.

New trials have started or will start shortly in the epithelial cell arena for different forms of epidermolisis bullosa, after quite a long interval from the first reported positive results (De Rosa et al., 2013). Initial promising results were reported at the conference (Michele De Luca, University of Modena and Peter Marinkovich, Stanford University). May Griffith (Linköping University) reported on new biomaterials for cornea bioengineering and Graziella Pellegrini (University of Modena) reported extensively on follow up and new developments for corneal regeneration by means of cultured limbal stem cells, both for total unilateral and partial bilateral ocular burns (Pellegrini and De Luca, 2014), which recently received conditional market authorisation. The exciting possibility of using a different source of stratified epithelium, such as the oral mucosa, for complete bilateral corneal destruction was also presented as a very preliminary observation.

4. …and where there is a longer road ahead

Progress is being made at a rapid pace for certain neurodegenerative conditions such as Parkinson's disease and multiple sclerosis (MS), although based on different approaches. In the first case, the localized nature of neuronal damage suggested more than a decade ago that cell replacement therapy was a pursuable option. Roger Barker (University of Cambridge) presented an outstanding overview of research over the last twenty years, starting with the pioneering transplantation of foetal midbrain, to more recent approaches using neural stem cells and ending with some of the challenges that the field currently faces and how they may be resolved (Barker et al., 2015).

In contrast, MS, like most degenerative diseases of the central nervous system, affects extensive regions, making a complete cell replacement approach a major challenge. However, MS also well exemplifies how crucial it is to understand the molecular pathogenesis of a specific disease in order to devise meaningful and possibly efficacious therapies as discussed by Robin Franklin (University of Cambridge) and Gianvito Martino (San Raffaele, Milan). As mentioned above, localized versus widespread distribution of tissue damage remains a crucial issue in determining feasibility, outcome and how rapidly benefit may be reached. In this respect, another example reported at the conference was cell therapy for a localized form of muscular dystrophy (oculopharyngeal), which results in a modest but partially efficacious engraftment (Gill Butler-Browne, Myologie, Paris) (Périé et al., 2014), whereas systemic delivery of donor cells to patients affected by Duchenne muscular dystrophy, while safe and well-tolerated, produced a level of engraftment that was too low to produce significant efficacy (Giulio Cossu, University of Manchester), presumably due to the severity of the disease and the advanced age of the patients, selected for safety reasons (Cossu et al., 2015). Moving from skeletal to cardiac muscle, the landscape does not change: in this case, many clinical trials have been carried out in the past (Assmus et al., 2015) and were briefly described at the Conference. Simple cell transplantation is unlikely to be efficacious for either acute or chronic heart diseases. Indeed, different strategies were presented by Kenneth Chien (Karolinska, Stockholm) and Stefanie Dimmeler (University of Frankfurt) ranging from delivery of modified mRNA or miRNA to promote endogenous regeneration (Sahara et al., 2015) to in vitro models of various cardiac diseases created with induced pluripotent stem cell-derived cardiomyocytes (Joseph Wu, Stanford University) (Ebert et al., 2015). Likewise, in the case of muscular dystrophy, strategies to correct neighbouring resident nuclei (taking advantage of the multinucleated nature of the tissue) and combination with other gene/drug therapies appear as a possible way forward to overcome the major hurdle of poor engraftment.

The scientific session on bone raised many issues and touched upon controversial topics. The bone marrow contains, in addition to the haematopoietic stem cells (HSCs), another population of adherent, clonogenic cells that have the ability to generate bone, cartilage and marrow fat; i.e., the cell types of the organ where they are resident. Such cells, usually referred to collectively as "mesenchymal stem cells" should rather be termed "skeletal stem cells" since they are specifically derived from bone (Bianco and Robey, 2015). In fact, cells with similar characteristics but different potency have been identified in many tissues of mesodermal origin. Despite their different specificities, such cells, are being utilized indiscriminately in hundreds of clinical trials worldwide, irrespective of their origin, and for a plethora of different diseases based on alleged immune modulatory and anti-inflammatory paracrine effects, often if not always in the absence of any real pre-clinical evidence, bio-distribution studies and rigorous endpoints to evaluate their efficacy (Bianco, 2014). The speakers of this session (Pamela Gehron Robey, NIH and Paolo Bianco, University of Rome) reiterated the clear difference between trials using these cells for repairing congenital or acquired diseases of cartilage and bone and the remaining, far less defined, questionable trials. The latter unfortunately

tend to "evolve" progressively into uncontrolled and unapproved treatments offered by private stem cell clinics of questionable reputation to patients with incurable diseases, unable to make informed and non-emotional decisions. Even with rigorous trials, an accurate characterization of bona fide "mesenchymal stem cells" revealed that the preparations are significantly heterogeneous depending on the centre producing them. Nevertheless, positive results in repairing long bone defects (in conjunction with appropriate biomaterials) were reported by Frank Luyten, (Leuven University). A careful analysis of the pathogenesis of fibrous dysplasia also led to an important conclusion: if the underlying molecular mechanism is fully understood and drugable, cell replacement is not an obligatory route (Paolo Bianco, University of Rome).

5. The ethics of cell therapy

Clearly then, cell therapy and regenerative medicine in general raise a number of ethical, economical and regulatory issues that were addressed in an ad hoc session. As a general introduction to this very complex landscape, John Harris (University of Manchester) took lead from vintage and recent cases such as in vitro fertilization and germ cell genome editing (Chan et al., 2015), to discuss how science and technology should harness public support while deflecting the emotional reactions that may affect the development of the field and its impact on patients' expectancies and their quality of life.

This consideration leads to the subsequent question; i.e., how do we make appropriate judgments on what is best for the "public good" and eventually help inform the decisions of policy makers in such a rapidly evolving field? David Napier (University College London) offered an example by discussing how and why scientists, bioethicists and economists should prioritize highly individualized and very expensive therapies, whose development impacts directly or indirectly on the general population. Setting aside the unregulated stem cell "therapies," the conundrum presented by the social and ethical justification for these new therapies remains evident. It was pointed out, however, that if found to be really efficacious, these therapies would actually lead to a significant economic benefit by eliminating the long lasting and expensive palliative therapies, and returning patients to a normal and productive life. Finally, from a legal standpoint, the advancement of regenerative medicine, while protected by "The right and liberty of scientific research," as explicitly recognized by the Constitutions of several European countries and by the European Union, impinges on the liberty and dignity of those involved in scientific research and experimental trials. Amedeo Santosuosso (University of Pavia) underlined how scientific research should not supersede the liberty and dignity of patients (and relatives) involved, and experimentation must be carried out according to rules accepted within the scientific community. These rules should guarantee that patients are not exposed to avoidable and harmful risks, especially without a fully open and understandable informed consent. Therefore, legislators cannot impose (within the constraints outlined above) technical and medical standards to researchers and physicians, nor should the judiciary impose administration of a non-validated, unapproved experimental therapy. The legal aspects are obviously very complex and challenging not only for the scientists, who have to offer safe criteria to the community, but also for jurists and courts, who must accept that rights (even fundamental ones) do not necessarily come first (Santosuosso et al., 2007). Clearly, a single session in a meeting could not possibly address all the important legal and ethical issues that cell therapy faces and will face in the future, but it is of fundamental importance to bring together the different communities and encourage them to openly discuss these overarching issues.

6. Conclusions

The meeting could not cover all the different areas, given the limited time available and the need to discuss in depth the complexity and the specificity of each individual therapy for a number of tissues/diseases. However, some generally applicable messages emerged. The first and most obvious conclusion is that a "one serves all" cell therapy does not and will not exist at least in a foreseeable future. On the very positive side, a number of remarkable achievements were reported, as well as possible solutions to address cases where success is still to be achieved. The conference also highlighted the important socio-economical and ethical implications of cell therapy, which also poses complex but not unsolvable problems.

We all hope, in fact, that in a not too distant future, consolidated, economically feasible, life-saving cell-based therapies will be available to treat an ever-increasing number of genetic and acquired diseases.

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