



A brief definition of regenerative medicine



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‘There are already a lot of definitions, but all are lengthy and not the sort of thing scientists, start-ups or advocates can say succinctly when a pharma executive, government minister or member of the public asks for clarification.’

While it could be said that regenerative medicine is what this journal publishes, that would be cyclical. It could also be claimed that most people interested in the field have a good grasp of what is entailed, and this is probably correct. But, as the field grows and there is a need to carry governments and public opinion along, it is probably worth having a simple explanation of regenerative medicine. And, it is simplicity that is the nub of the matter. There are already a lot of definitions [1–3] but all are lengthy and not the sort of thing scientists, start-ups or advocates can say succinctly when a pharma executive, government minister or member of the public asks for clarification. Here, we address this and the origins and relationships that help to define the field.

One of the complications is that regenerative medicine has grown out of a good deal of prior activity. This includes surgery, surgical implants, such as artificial hips, and increasingly sophisticated biomaterial scaffolds. It also draws on hospital procedures such as bone marrow and organ transplants and it relates to tissue engineering. There is no absolute cut-off in the transformation of these into fully developed regenerative medicine but they each leave residues of their input that can mean the patient is not capable of being termed ‘of natural health’ with respect to the treated condition. Organ transplants often demand immune-suppressing drugs and metal hips can become loose with time, engineered tissue scaffolds can provoke inflammation and bone marrow sources are variable mixtures that also can be contaminated quite easily by the nature of the cell aspiration procedure.

The central focus of regenerative medicine is human cells. These may be somatic, adult stem or embryo-derived cells and now there are versions

of the latter cells that have been reprogrammed from adult cells so that both can be conveniently collected under the heading of ‘pluripotent cells’ [4,5]. There appears to be a progression in interest through this sequence. It is driven by the limitations in availability of most specialist somatic cells and the restriction in the expansion of adult stem cells together with their heterogeneity from sources such as bone marrow. Human embryos are not an ideal source from a technical point of view, leaving aside the ethical and moral issues. For this reason, obtaining pluripotent cells in another way is attractive. This progression entails the transfer of genes to human cells [6] and this could bring regenerative medicine and gene therapy closer.

Though inevitably the pioneering phase leading towards regenerative medicine has been marked by some failures, there are now sound commercial products for skin ulcer and sports injury damage to the cartilage of the knee [7]. There are also exciting developments with respect to treating patients with bladder dysfunction [8]. These therapies use either autologous or allogeneic somatic cells and, in the case of skin and bladder, the products have a biomaterials component. The outcome of therapy with adult stem cells is at present less clear because the status of these cells is being debated [9], but in the end it will be proof or otherwise of therapeutic outcome that defines their importance.

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For the present, most of the developments with embryo-derived cells are as pure cell therapies, although treatment of age-related macular degeneration is likely to involve a scaffold [10]. It is probable that in time more therapies involving embryonic stem cells and temporary scaffolds will appear and certainly where structural tissue is demanded it is hard to see cells

alone succeeding. However, it is probably inevitable that for the present there will be a distinction in journals and interest groups between the biomaterials community and that concerned primarily with advanced cell approaches. Indeed, there is in some cases a philosophical difference. Where biomaterials scientists are affected by the interest in nanotechnology, they may be drawn towards those who envisage future medicine heavily reliant on man-made nanodevices [10]. By contrast, the vision of those focused on cells tends to be more towards emulating nature's capacity, with the minimum of artificial material present. That said, medicine as a whole will not wish to pit cell-based regenerative therapy against other options of molecular medicine and new technologies such as nanomedicine, but rather to achieve the best blend. The 'regen' industry as we have described it [11] will integrate human cell therapy with gene-based methods, biomaterials and molecular medicines. In the medium term, there are a number of major medical conditions, such as heart failure, insulin-dependant diabetes, spinal cord injury, Parkinson's and possibly Alzheimer's diseases, which appear to be addressable via cell-based therapies. There are many more that, although they affect fewer people, are terrible in their consequences, have no present effective treatments and should be susceptible to human cell-based approaches.

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Clarity on the nature of regenerative medicine will be vital in an industrial context. We have noted the relationship of regen ventures to biotech start-ups [11]. For the more sophisticated products of regenerative medicine research, we concluded it is likely that most start-ups will need the deep pockets of major pharmaceutical, healthcare or device companies. Human cells are a rather alien concept to pharma people used to molecular medicines. However, those biopharmaceutical protein companies using mammalian cells are very familiar with cell banking. They are also knowledgeable about culture advances to enhance performance in producing products and improving their molecular properties. If those

pursuing regenerative medicine can use this relationship and be clear on what is involved there is at least a conceptual bridge. Pharma is already much interested in using embryonic stem cell-derived material for drug discovery [12] and toxicology studies [13] and, while not regenerative medicine, it is building bridges with regen start-ups. It is also the case that the exceptionally high cost of some therapeutic proteins will mean pharma will not be particularly surprised if the human cell therapeutic preparations are also of high cost. The pharma sector has not as yet had good experience with biotech companies in gene-based medicines and will move with caution where it appears to be involved. However, they do use gene transfection to enhance cell properties in tightly regulated processes. They will struggle with a business concept in which cells may only be required once for lasting benefit compared with the majority of protein therapeutics, a situation for cells more like the sale of a medical device. Indeed, a few device companies concerned with acellular repair are already active in collaborations with regen start-ups. In a future of rapidly growing demand for medicines to address degenerative diseases all this need not be a disincentive to pharma–regen linkage but it will have to be clear that regenerative medicine can justify high prices where appropriate and is capable of routine production to high standards of safety and efficacy. That means being able to convey accurately what it entails.

A successful regenerative medicine centered on human cells could be a 'disruptive technology' because it would potentially replace a number of major molecular pharmaceuticals and medical prostheses. For example, stem cell-derived β -islet cells can potentially replace a patient's requirement for insulin injections [14]. For this reason, it would be valuable if human cells can be perceived as a logical extension of the progression from small to macromolecules. Like proteins, they could create new opportunities and a safety net for pharma when chemical pharmaceuticals are suffering many late-stage clinical failures and the expiry of their key patients. Even biopharmaceutical proteins, and especially antibodies, are becoming a crowded commercial area. Vaccine production using attachment cells is particularly close in respect of some upstream aspects of cell culture scale-up and, in terms of commercial parallels, vaccine therapy generally involves only one or a few injections in a lifetime. Similarly, regenerative

medicine that goes beyond cartilage regeneration to aid structural restoration can be seen as a logical development from prostheses. Again, this should help build up a bridge between regen and pharma.

We have focused on human cell-based therapy but it is worth further emphasizing the important and growing linkage between gene therapy and regenerative medicine. Cell therapy represents a way of placing genes in cells, checking the outcome is safe and then implanting the cells into patients. The current interest in programming adult cells back to induced pluripotent stem cells is driving the gene–cell linkage and the work of ReNeuron [15] in using a genetic approach to immortalize a fetal neuronal cell line for the potential treatment of stroke is illustrative. Here too is an example of checking the safe outcome by selecting cells that have the gene placed at a suitable point in the genome. Although the regulatory challenges are increased by genetic manipulations, this linkage of cells and genes could open up new options for regenerative medicine.

More difficult to place is the use of activator molecules, which applied, once or a few times, can influence the outcome to cause regeneration. The use of bone morphogenic protein-2 growth-stimulating factor from the Stryer company and erythropoietin from Amgen are examples of highly successful commercial materials. A further illustration is provided by the products of Renovo, which use macromolecules such as recombinant transforming growth factor $\beta 3$ and small molecules such as 17β estradiol to favorably enhance skin healing without scar formation. In technology terms, these are all examples of molecular pharmaceuticals but their effect can be regenerative. They differ from doses of antibiotics, which are restorative of health but not regenerative. Other molecular medicines will often be an important complement to human cell-based medicines, for example, drugs to control blood pressure could prevent stem cell-regenerated heart tissue from being further damaged.

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A final reason why regenerative medicine needs a clear position is that, so far, it is hardly on the radar of the working-level healthcare

bureaucracy, although in the USA [102], as in the UK [103], governments are now aware of its importance. The medical community sees the claims, some far fetched, but is preoccupied with disease today and heavily pressed by the massive marketing of the molecular pharmaceutical sector. Even though those drugs can often only slow disease and not infrequently have severe side-effects, they are available and meet a need. Government statistics are weak on the costs of disease that occur beyond hospital treatment and it is here that human cell-based medicine has great potential versus long-term use of molecular medicines for chronic conditions. Thus, the explanation needs to focus on the value of the regenerative element.

The regen industry will probably utilize small- and large-molecule activators of the kind mentioned above and will embrace genetic modification of the cells. However, these aspects represent different technologies, some already well established. Regenerative medicine itself has as its principal focus human cells either implanted into patients or present already and regenerated by agents from those different technologies described above.

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Classically, ‘regeneration’ is used to describe ‘the process in humans whereby lost specialized tissue is replaced by proliferation of undamaged specialized cells. The process differs completely from the axial regeneration of amphibians...’. It is presently limited in humans to just a few tissues, such as liver, leaving aside normal replacement of individual cells in, for example, epidermis and intestinal mucosa [16]. In this regard, the aim of regenerative medicine is to regenerate more fundamentally by the provision of cells, particularly stem cells that can stimulate wider regeneration. Equally in classical terms ‘repair is the replacement of lost tissue by granulation tissue which matures to form scar tissue’ [16]. Yannas has expressed the distinction in a particularly clear way: ‘Organ regeneration is distinct from organ repair as an endpoint of a healing process following injury. Repair is an adaptation to loss of normal organ mass and leads to

restoration of the interrupted continuity by synthesis of scar tissue without restoration of the normal tissue. By contrast, regeneration restores the interrupted continuity by synthesis of the missing organ mass at the original anatomical site, yielding a regenerate. Regeneration restores the normal structure and function of the organ; repair does not' [17]. Since the ultimate aim of regenerative medicine is to return the patient to full health with respect to the particular condition, 'repair' falls, we feel, within earlier technologies such as surgery. Repair is invaluable but the consequences of repair can be unpleasant, for example, internal and external scarring. In most cases, the aim of regeneration will be to restore a function that has been impaired but it could also address congenital abnormalities, such as thalassaemia, absence of corneas or so called 'hole in the heart' cases, where the normal functions were initially absent.

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And so we return to the way of explaining the field. Above all it must be simple. The explanation must avoid confusing the audience. If it includes tissue engineering, genetic engineering and molecular activators and so on the danger is that it will lose focus. The techniques used will also change with time. If the enquirer asks for more, then, depending on their background, there are many different kinds of detail that can be added. Equally, though it would be valuable to lay emphasis on the contrast with molecular medicine and its need for 'repeat prescriptions' for chronic conditions, this too can be left to elaboration. Of the lengthy definitives we have used, that of Greenwood *et al.*, is probably most suitable as a starting point: 'Regenerative Medicine is an emerging interdisciplinary field of research and clinical applications focused on the

repair, replacement or regeneration of cells, tissues or organs to restore impaired function resulting from any cause, including congenital defects, disease, trauma and aging. It uses a combination of several technological approaches that moves it beyond traditional transplantation and replacement therapies. These approaches may include, but are not limited to, the use of soluble molecules, gene therapy, stem cell transplantation, tissue engineering and the reprogramming of cell and tissue types' [3]. This provides a basis for a short explanatory sentence. For the reasons given, we have deliberately not included 'repair' but have covered instances where normal function has been 'established' for the first time. We have also added 'human' to qualify the 'cells, tissues or organs' because, although other options are possible, such as using porcine-derived islets, they can be accounted for without direct mention. So the explanation can simply be: 'regenerative medicine replaces or regenerates human cells, tissue or organs, to restore or establish normal function'.

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