



# Regenerative medicine bioprocessing: the need to learn from the experience of other fields



Chris Mason<sup>†</sup> &  
Mike Hoare<sup>1</sup>

<sup>†</sup>Author for correspondence  
<sup>1</sup>Regenerative Medicine  
Bioprocessing Unit, Advanced  
Centre for Biochemical  
Engineering, University  
College London, Roberts  
Building, Torrington Place,  
London WC1E 7JE, UK  
Tel.: +1 207 679 0140  
Fax: +1 207 209 0703  
E-mail: [chris.mason@ucl.ac.uk](mailto:chris.mason@ucl.ac.uk)

Here, we first examine whether lessons may be learned for autologous cell processing from other fields addressing personalized targets. We then summarize how manufacturing innovations in diagnostics give general pointers to cell and engineered tissue processing for allogeneic and autologous cells. This editorial analyzes the bioprocessing issues specific to regenerative medicine, such as the crucial interface with patients and clinicians and the impact of the distinctive regulatory framework. We conclude by summarising the desirable characteristics of future regenerative medicine bioprocessing.

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## Personalized products in other sectors & autologous cell processing

A field close to autologous cell regenerative medicine, in terms of dealing with differences between individuals, is the treatment of patients in conventional healthcare. As with all medicine, regenerative medicine faces the challenge of how much must be customized and how much can be standardized. The medical profession has moved from an almost totally customized approach towards treatment to one that now embraces varying degrees of standardization. This is in part economic, but may also lead to a better outcome for the patient than the classical customized one: a standard procedure can ensure that treatment does not rely solely on the memory of a busy physician. Bohmer noted that customized treatment can be separated completely from a standardized one on the basis of early-stage decisions or parted later when the need becomes evident [1]. Having a separation scheme allows expensive specialist human intervention to be focused on the non-standard patient. Whenever a division is made, data that allow a clear decision are crucial, and the higher the proportion of patients that require a custom approach, the higher the overall cost of all units processed. Autologous cell and tissue processing poses similar challenges [2]. There will

be cell outliers from some people that, for a number of reasons, may fall outside standard processing conditions and will need specialist intervention in their bioprocessing. As in treating patients generally, it is likely to be possible to apply common limiting values to some of the factors affecting the bioprocessing of human cells, such as control of shear, while others may need greater customization, such as the addition of stimulating molecules. Patient variation also poses challenges in their imaging by methods such as magnetic resonance imaging (MRI); methods have been devised to normalize these and enable a better distinction between healthy and diseased tissue. Nyul and colleagues described an approach that relates the image histogram to mean values established previously [3].

At first sight, recent developments in mass production appear to be relevant. It is now increasingly common in fields such as automotive engineering and computing to be able to purchase personalized products. By new organizational approaches, these can be supplied at near the mass production price but are tailored to the desires of individuals. However, the approach rests upon the intrinsic availability of a finite range of standard stock, such as car components of different body color and engine size or of computer alternative hardware and especially software variants. The mass customization entails mixing and matching these stocks. Thus, the intrinsic difference compared with regenerative medicine is that the 'stock', which is the individual human cells, is almost infinitely variable. If those differences are reduced, the cells will tend towards allogeneic. A more recent mass customization development in another industry has a somewhat greater bearing. Developments in computer and machine technology are allowing clothing, such as suits, to be customized without the costs being as high as for conventional personal tailoring [4]. Here, the human variations are very large with many permutations. The material from which the clothing is cut is still of a limited range of variations, although the approach does offer the pointer that if a technology can use the power of modern computation, it may be possible to achieve realistic costs when each item is individualized. Nevertheless, there

must still be a low-cost device technology to which the computation interfaces. The method described by Dekker and colleagues also applies to modeling the individual human body for medical purposes, such as drug dose decisions, and this philosophy will also have relevance [4].

Where a philosophy of a ‘market of one’ [5] may be very relevant to regenerative medicine is in the approach to the nature of the business model and the bioprocess thinking that underlies it. Initially, the use of allogeneic cells appears much more attractive in simplifying the technology. However, by the same token, it will make competition more intensive globally. By contrast, the ‘market-of-one’ approach is very demanding in organizational terms and those, such as the computer company Dell, that have developed a built-to-order products capacity with related delivery have had to underpin it very effectively. This has demanded a well-integrated supply chain, advanced information systems from order entry and exceptionally strong support from delivery and logistics partners. The typically web-based systems used must be able to move quickly from an order to inventory level check, component reservation, calculated manufacturing time and a delivery date. The actual manufacturing control must be flexible, with a decision in place at each process step and information collected up to the minute into manufacturing execution systems (MES). Each product in an autologous cell bioprocess line will be distinct, therefore, the enterprise resource planning (ERP) system must be updated constantly. When a customer (in the case of regenerative medicine, the surgeon or clinician) logs onto the company’s website, they would require real-time processing data, so the system must be highly accurate. Orders are delivered individually, not as palletted loads, and timely delivery is critical. Since there is no retailer role of a conventional kind other arrangements, such as service agreements, are required to sustain outreach. Such market-of-one companies have to achieve a high focus on organizational performance via training and productivity and quality must be uniformly high. These developments will not occur immediately in regenerative medicine, although a progression towards them can be envisaged. For example, initially, an engineered artery is likely to be a standard material but, given that the equivalent of 600 miles a year of tube would be needed globally to replace the use of vein autografts, there will be scope for more personalized material; diameter variants to account for the difference between men and woman, and length variations to account

for the projected position of implantation. The degree of segmentation will be likely to influence the level and type of any automation. This is because the justification of classical automation, to allow high-throughput production of identical products, will not then apply, and any automation must be able to address the variants easily. If human somatic cell nuclear transfer (SCNT) were ultimately to allow ‘personalization’ of embryonic cells, it would provide a strong incentive to pursue a market-of-one approach.

In looking for other analogs for human cells, biological feedstocks, such as agricultural materials, represent a sector where variability has been a long-term source of technological difficulty. In most cases, variability is between large items, such as fruit, fish and meat carcasses so that, for example, the imaging methods are not directly relevant to cell-scale materials, although some may apply to tissue constructs. More directly applicable may be the means of dealing with variability by computer-based methods. For example, the use of knowledge-based control systems to deal with the inherent variability of agricultural products also applies to human cells [6]. Similarly, the training of robots to assemble food products, such as sandwiches and pizza, may be relevant [7].

#### **Manufacturing innovation pointers from other sectors applicable to all regenerative medicines**

Although, currently, the preparation of units of human cells and tissue is a highly specialized activity, it will inevitably conform to the forces that are shaping other manufacturing activities. These include the need to be able to launch new products quickly and to achieve a rapid adjustment capability as markets change. Since human cell science, especially that of stem cells, is changing rapidly, there is a requirement for manufacturing to be flexible. Finally, there is a need to be able to quickly alter the quantity of product produced. As with all sectors, there will be an inverse logarithmic dependence of scale of global manufacture and price [8]; just as penicillin production began at a low level with a high unit value and the price fell with overall scale and inherent competition, the same will be true with human cells and tissue, even if the quantities are much smaller.

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The field of medical diagnosis offers some useful insights on automation to address the need for throughput and the impact of competition. Tomar noted that early automated instruments mimicked manual methods, but later took advantage of newer technologies [9]. These allowed laboratories to meet the large increase in testing demands at lower cost per test and without increasing staff. From the 1950s to the 1980s, individual automated instruments still remained separate, but then total laboratory automation (TLA) installations began to be developed. However, Tomar noted that whereas the payback period for laboratory equipment was typically 2–3 years, the equivalent time for TLA may be 5–7 years and administrators become concerned about obsolescence over this timeframe. He emphasized that a significant part of the problem has been the lack of agreed standards on issues such as computer codes, bar codes and electrical systems, a deficiency now beginning to be addressed. The same considerations will apply to regenerative medicine bioprocessing. Tomar also makes the point that, over time, diagnostic laboratories will need fewer medical technologists and more computer specialists and engineers, and this too will apply to regenerative medicine. The changes that have been occurring in clinical laboratories (for example, Conn and Snyder [10]) may give a clue to how regenerative medicine bioprocessing will develop. The trend has been for diagnostic testing to be viewed increasingly as a commodity rather than a medical service. As this comes to pass in regenerative medicine, cost cutting will become a necessity and there will be pressures to consolidate activities in larger centers that can achieve savings due to throughput, although this will rest on whether storage stability for cell feedstock and final products is adequate. As the regenerative medicine field develops, it is likely that contract manufacturers will grow to specialize in the production of materials for clients that wish to retain a focus on the science. Such contractors will require particularly robust technology since it will be the basis of their business. Equally, if major healthcare companies enter the field, their early bad investment experiences suggest they will need to give more attention to the special demands of regenerative medicine bioprocessing, which differ significantly from molecular pharmaceuticals. In relation to finding bridging, medium-throughput automation, the use of robots in fields such as genotyping is of interest since it illustrates the capacity of robots to deal with flexible numbers of units once an initial investment is made [11].

Classically, manufacturing advances commenced with a progression to mass production (to reduce cost), then lean manufacture (to raise quality at still lower costs), followed by flexible manufacture (to produce a variety of products in the same system). The dangers of flexible manufacture (being expensive to cover all options and also being susceptible to obsolescence) have led recently to arguments for reconfigurable manufacture, where core process modules and related software can be rearranged quickly and reliably [12]. Since regenerative medicine companies are often pursuing several target tissues, a capacity to ‘mix and match’ processing units and software would aid flexibility and profitability.

### Distinctive features of regenerative medicine

#### *Patient & clinical interfaces of bioprocessing*

Regenerative medicine using autologous cells differs from previous medicines, such as small-molecule drugs, biopharmaceuticals and allogeneic cells, in that there is a much more intimate connection between a clinician harvesting the cells, those processing them and the surgeon or physician who implants the material. The dose form of a molecular drug is a matter of concern to the manufacturer, but the format in which human cells are provided for therapy will be a more direct component of the processing. For cell expansion with allogeneic cells, there is no particular interface with the person deriving the original cells, however the interface with the physician or surgeon, in terms of administration of the expanded cells or matured tissue, is much closer than for most molecular medicines, except for those that demand infusion. In addition, it can be important to match the therapeutic material to the site of use. More subtly, the nature of the disease state in the patient’s tissue may influence how implanted cells or tissue are applied and the ‘whole bioprocess’ philosophy must embrace consideration of such issues.

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To address the severe challenge of preserving sterility, it will help if the bioreactor in which an engineered tissue is to be produced is also the vessel in which it is supplied for patient treatment. If this is not possible, minimum or no

manual intervention is desirable in transferring material to the final container. If the tissue is difficult to extract from its container, it will not be favored by the clinician or surgeon. Conversely, the form of engineered tissue could enhance and change the way surgeons operate. For example, cardiac surgery is already beginning to be performed by robotic systems [13] and more reproducible material, such as engineered artery, provided in a suitable cassette would make the use of robots for by-pass surgery much more attractive than with material from the patients' veins with tied-off tributaries (side branches). Surgical robots are also being applied to neurology to achieve very high precision [14] and, in principle, linkage direct to a supply of cells provided by automated expansion could avoid all human contact. However, it is not necessarily the case that a more sophisticated product will be best. For example, if a full-thickness skin is prepared, rather than a temporary skin substitute, it must be harvested and applied by a surgeon rather than a specialist nurse practitioner, thus the cost rises and the throughput of treatment falls.

It is essential that a manufacturer is not held responsible if poor handling at the user site is the cause of product damage. In addition, it is vital with autologous material that the initial harvesting of material from the patient meets the same high standards and that confusion between material from different patients is avoided at all stages. This requires training to embrace not only mainline bioprocessing staff but also those who harvest cells and who ultimately use the cells or engineered tissue. Equally, if the delivery method for the cells does not safeguard the physical and biological state of the cells, they will be unacceptable as therapeutic material. This can be assisted by aids that check material identity and its state. In terms of identifying cells and their source, there are strong parallels with what is now performed to avoid confusion between patients themselves and their diagnostic samples. In the past, bar coding has been used, however its need for close line-of-sight reading and the possibility of error due to bending or surface damage does not make it ideal. As a result, there is considerable interest in radio frequency identification (RFID) systems. These incorporate electronic devices, called transponders, and reading units. The transponders, or tags (as they are known), are attached to the items to be identified. The tags do not communicate continuously and instead only send out responses on receipt of a coded request, thus saving wasted battery

power. The method does not require line of sight and is being examined to increase efficiency in the supply chain for short shelf-life goods [15]. There is particular interest in healthcare applications [16]. In such fields, any handling out of tightly temperature-controlled conditions is potentially damaging and RFID can also log this. Harrop noted the use of tagged Luer fittings to prevent this, but the correct linkage confirmed by an electronic handshake and the evidence of correct procedure is inherently easy to record to a computer. He noted the value of RFID in connecting 'islands of automation' and this is likely to be valuable in the semiautomation that will characterize regenerative medicine for the foreseeable future. The current range of RFID is approximately 10 m for tags without batteries but ranges up to 700 m with battery systems being developed.  $\gamma$ -ray irradiation of the type used to sterilize disposable components destroys the silicon chips used currently, although versions that avoid this are reported [16]. Active RFID chips (those with an internal power supply) can be integrated with sensors, such as those measuring temperature and humidity [17].

Variations in cell quality and quantity from individual patients will have a major impact on autologous cell progressing. At the front end of the process, the level of contamination of bone marrow biopsies reported ranges from 3 to 26% and, thus, has a profound impact on bioprocess consistency [18–21]. In addition, there is evidence of great variation in the bone marrow material taken from patients. Phinney and colleagues examined mesenchymal stem cells from 17 healthy donors and found a 12-fold variation in growth rates *in vitro* [22]. There was no correlation with age (19–45 years), however differences occurred in multiple aspirates from individuals and even in left and right aspirates on the same occasion, suggesting cellular heterogeneity due to harvesting. This will either need to be countered by automated aspiration or allowed for in processing. An effective approach will need to embrace an improvement in bone marrow harvesting methods as much as those of the subsequent stages. Similarly, the means by which human embryonic stem cell lines are derived must be improved to achieve higher efficiency and greater consistency. Likewise, somatic cell nuclear transfer (therapeutic cloning) will probably require robot-assisted manipulation if it is to be successful and efficient. The manual procedure demands a high degree of skill, for example, the microinjection of a

somatic cell nucleus into an enucleated egg is exceptionally difficult in part owing to its small size (50–100  $\mu\text{m}$ ). Recently, the creation of a single-cell manipulation-supporting robot has been described [23]. Its aim is to reduce the coordination burden on the operator, who typically has to manage eight x, y and z direction controllers of the micromanipulator as well as observing the result by high-resolution microscopy. The cell shape is deformed during microinjection and, in order to minimize the physical stress on the cell, damage to the outer membrane must be minimized. Thus, as in the main bioprocessing steps, the issue of shear-related effects is crucial and a degree of automation can reduce the danger of an unintended hand movement. It is also susceptible to the collection of a permanent record of the force used so that the procedure can be optimized over time. Related studies of mammalian cells in microfluidic systems [24] will increasingly mean that other initial cell manipulation steps prior to downstream expansion stages after micromanipulation will be susceptible to automation. They will demand careful characterization.

Even with the elimination of avoidable variables in human source material, there will remain variations due, for example, to age [25,26]. Haddad and colleagues have identified several potential specific gene clusters, one of which correlated with T-cell proliferation and may potentially be used to predict cell expansion and possibly, in the future, to rescue poorly performing patient samples [27]. This, and similar genetic analyses, are currently being applied mostly to cell culture, but will need to be conducted for other bioprocess operations since these can also cause cell stresses.

As well as being provided in a convenient format, autologous cells or engineered tissue must be available to a schedule workable for the physician or surgeon. For engineered tissue especially, this will ultimately mean the surgical team will be able to access, although not change, the bioprocess status of a patient's material so that their scheduling gains the maximum efficiency. It may be possible for the process center to adjust the schedule. For example, by lowering the temperature, it is possible to slow the growth rate of cells in engineered tissue to match the desired window for use. Just as the clinician or technician harvesting initial cells must be trained to meet the high standards needed to achieve good tissue practice, so must those dealing with reimplantation if high whole-bioprocess performance is to be achieved.

### *Impact of the regulatory framework on bioprocessing*

The regulatory demands for regenerative medicine materials are potentially greater than for molecular pharmaceuticals and much more severe than for most other industries. Although some therapeutic materials will only contain the products of cell synthesis, the central ones will involve living cells that can reproduce once implanted. Therefore, compared with molecular pharmaceuticals other than genes, there is a potential for greater long-term damage if the material is not in the correct state. Such are the complexities of cellular processes that the definition of this state is difficult, especially when it has to be achieved noninvasively [2]. The regulatory authorities recognize the challenge but inherently, as commercial developments proceed, they will be obliged to tighten their control progressively. The US FDA has now formulated clear guidance on good tissue practice [28,29]. Essentially, this seeks to balance the degree of regulation against the risk of individual categories of material and, broadly, the more bioprocessing applied, the greater the degree of regulatory control, since the opportunities for contamination and adverse conditions increase. The rules do acknowledge the particular challenges of regenerative medicine, such as the inability to apply terminal sterilization to the product and the relative slowness of some of the analytical outcomes. Nevertheless, they emphasize the need for sophisticated current good tissue practice (cGTP) systems to fully characterize materials in order to achieve the consistency that will be the hallmark of good products. For example, it will require the preparation of several hundred standard operating procedures (SOPs) also covering materials used. The current lack of a single global regulatory framework, and particularly the uncertainties in Europe, are a serious constraint on the new field. The kind of bioprocess systems aforementioned and their linkage via computer-based methods, appear likely to be essential for all but an early-stage cottage industry. The potentially large amounts of operational, environmental and analytical data both on- and off-line will pose a challenge in providing information for managing bioprocesses as well as informing the physician or surgeon on the readiness of material. Data management is a problem faced by the whole biomedical community, from basic systems biology to clinical evaluation of multiple patient data. In the case of bioprocessing, as in all pharmaceutical sectors, the data-processing systems will need to be validatable [30].

Although this paper is not concerned directly with issues such as reimbursement by insurers or acceptance of regenerative medicine costs by public sector authorities, these are plainly issues where the user and intermediate organizations have a large impact on the progression from manual to more automated bioprocessing. The necessity to establish acceptability before large automation investments favors manual approaches; however, given that acceptance, there is then a considerable incentive to automate to meet the price demands of those that pay.

In the processing of macromolecular biopharmaceuticals, conservatism in the purification methods used arises because pioneering a new separation technology through the regulatory process is very expensive and demanding. Conversely, a few bold and more established start-ups have used new technology to differentiate themselves. It is likely that regenerative medicine bioprocessing will demonstrate similar patterns.

#### *Progression towards automation*

From the aforementioned examples and lessons from other fields, it is possible to draw some conclusions regarding the likely nature of equipment and operating approaches for bioprocessing to be applied to regenerative medicine.

To progress from research-oriented process systems it will be necessary to give much more attention to aspects of design that address users, the needs of validation and the demands of efficient manufacture. Designs should make it easy for operators to comply with SOPs and for couriers to efficiently transport material without disturbing the condition of the content. The design must also be such as not to expose operators to risk, which could, for example, arise with autologous sources of cells. From initiation, design should have the needs of validation in mind. The FDA defines this as ‘establishing by objective means that a process consistently produces a result or product meeting its predetermined specifications’ [31] and this must extend to all components and feedstocks. Equally, all computer-related activity must comply with requirements, such as FDA regulations on electronic records and signatures [30]. In terms of design for manufacture, scale-out simplifies large-scale production by simply replicating what is performed with a single unit, but each unit requires its own monitoring and control, thus the reliability in a large number of bioprocessing units must be very high.

As indicated by Kino-Oka and colleagues for cell expansion [32] and Roos and colleagues for tissue formation [101], robotic methods offer a method of achieving automation that can be added to manual procedures. This is particularly so for procedures involving flat sheets of material. The ability to add extra robots enable growth in capacity to be added incrementally. It is also possible to keep some elements of the task manual where this is difficult or costly to roboticize. One consequence of this approach may be to make the manually conducted activities of rather low sophistication. This could cut costs, although it might also reduce the quality of input. Therefore, it will be necessary for staff to have multitasking skills. That may be advantageous to operators since semiautomation does not necessarily eliminate repetitive strain problems [33]. With more complex tissue geometries, there is considerable interest in computer-based automated methods of creating scaffolds, however, the subsequent medium addition may be less easily roboticized [2].

#### **Discussion**

At present, the systems for producing expanded human cells have considerable commonalities amongst themselves when using manual procedures, although existing semiautomated devices tend to be more cell specific. For engineered tissue, the few manufacturing systems have been even more material specific (e.g., Naughton [34]). It will be necessary to take a view on how much commonality the future systems can have and how to achieve integration of standard modular components that can apply to different tissue targets. With scale-out as applied to autologous cells, it will be particularly important to be able to diagnose problems in a large number of parallel systems and to raise reliability to a high level. It will also be necessary to take a view on where human operators are a source of unreliability and where their involvement is valuable in assessing the complexity, bearing in mind that, in routine processing, a degree of fatigue over the working day is inevitable. Archer and Wood introduced robotic systems for roller bottle culture and found that contamination levels, typically of 5% in the manual processing of bottles, was reduced to 0.2% by the use of the robotic system for cell culture and related operations, such as trypsinization [35]. The report also noted labor levels tenfold lower.

In situations such as human embryonic cell line derivation, somatic cell nuclear transfer and harvesting from bone marrow, we have argued

that humans supported by automation have advantages. We have also noted that, for autologous cells especially, the effective use of computing power will be important in achieving reliability and throughput at acceptable costs. In relation to this, artificial intelligence methods have recently been applied to choosing the most effective scheme for tissue engineering [36]. Low-cost computer-based methods demand the same need for modularization, integratability and capacity for easy upgrades in software as that for hardware. In turn, this indicates a need for process staff who can deal with such software or at least know how to specify it.

Since the nascent industry is inherently science centered, it will not initially have significant strengths in bioprocessing, automation and software engineering. Therefore, flexible systems that can establish a bridge from manual via semi-automation to automation will be valuable. While in theory, transfer of the production to low-cost countries is an option where manual operation could be sustained, in practice, there are factors that will restrict this. The development of the biopharmaceutical protein industry has occurred principally in the USA and Western Europe owing to the complexity of the materials and processes and also the availability of a supply chain of companies providing validated components. Human cell-based materials are even more complex and, in addition, the technology may be more country 'embedded' owing to the intimate links between clinical and process elements. In the case of small molecule pharmaceuticals, it tended to be the case that not very efficient processes were adopted because they were adequate to yield very high-value products, and if additional material was later needed, identical facilities of equally modest efficiency had the advantage of requiring less development. The greater complexity of macromolecular biopharmaceuticals has meant that efficient processes are much more critical and this trend will accelerate with regenerative medicine since product consistency is more difficult to achieve. The development of a relevant bioprocessing equipment sector will be important and is happening at present by adaptation, in the case of allogeneic human cell culture. It is based on earlier developments with mammalian cell culture, both in single bioreactors and in robot-operated large microwell systems. As always, at the beginning of a new technology, there is the problem that commitment by the supply companies is hard to achieve until the number of users justifies the developmental

effort. It is here that efforts to envisage more broadly applicable bioprocess systems will be helpful in encouraging them.

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The slowness of human cell expansion and especially of engineered tissue maturation means that capital items may be committed for long periods and lead to implicitly costly products. Minimizing these times and the number of stages as well as enhancing yields will help. The costs of quality clean room space per square area will also be high, thus compact processes will be attractive. Although medium costs are high at present, they tend to be matched by transport costs with products that have a very limited shelf life. Therefore, advances in longer term storage will be of considerable importance.

One of the factors that will influence the importance of automation versus manual operations is the extent to which an existing technology serves the purpose, albeit with disadvantages. For example, engineered arteries will need to offer real gains in order to replace the vein autografts now used, except in instances where no satisfactory vein is available. Since the latter have no cost, other than the fairly hidden extra surgical time required for harvesting and tying-off tributaries, the gains will need to come from slowly established advantages in terms of recovery times and life of graft. Therefore, in the shorter term, cost and consistency will matter. In other situations where there is no effective treatment, as in neurological conditions, the initial price chargeable can be relatively higher, although the demand for consistency will be exceptional. This will be achieved only by more rigorous bioprocessing and a degree of automation.

From the above, it is possible to summarize the desirable characteristics of regenerative medicine bioprocesses (Box 1). Above all, they must produce a good product and do so with high consistency, and lowered cost for many units of material. In addition to this, the performance must be reliable, which is served by the simplest and most elegant design: complex equipment that is difficult to assemble and maintain is always a recipe for problems and safety failures. In a new technology, with an

**Box 1. Desirable characteristics of regenerative medicine bioprocess design.**

- Yields a consistent, safe product.
- Achieves reliable operation.
- Easy to alter in throughput.
- Quickly set up and easily maintained.
- Easily displays process and product status.
- Applications to several products.
- Assures operator safety.
- Maximum degree of automatic control.
- Smooth progression from manual operation to automation.
- Yields lowest cost, consistent with required performance.
- Allows autologous cells source identification throughout.

unstable position in terms of global competition and the initial lag in clinical acceptance, a ready capacity to alter throughput will be important. Equally, an easy ability to view the status of the process and the product will be valuable. Although the danger of designs addressing several products is always that none will be optimal, such a capacity will reduce costs and enhance flexibility of output as commercial competition grows. Even for manually operated bioprocesses, it will be important that as many of the basic variables as possible, such as pH, temperature and dissolved oxygen tension (DOT), are under automatic control to set points so that human operators are not overwhelmed by the number of variables. Over time, an increasing degree of automation of all aspects is desirable and, in the case of autologous cell processing with its inherent scale-out, this will be especially so. However, the potential for high-development costs and major development problems in heavily automated systems pose considerable commercial risks. These are particularly severe with a new generation of medicines where venture funding must be concerned with a fast route to exit by floatation or acquisition. Since automation will later allow improved performance and cost, it will be essential to plan a route from manual operation via semiautomation to more extensively automated systems. Most current, manual processes operate on a 5-day working week with a 9am–5pm day, with all protocols based on this schedule. Given that robotic systems gain by being 24/7 systems, it will not be a good use of them if manual inputs constrain this. As aforementioned, the correct balance between automation and human intervention will be especially important with regenerative medicine owing to the complexity of the material. For autologous human cell-based

products, the variability of its patient sources and health status will be a particular challenge for automation. The degree of automation will ultimately bear heavily on the product cost, which will become ever more critical as the sector grows.

For all human cell-based materials, the safety of the operator is essential, and this is especially so for autologous human cell preparations where viral and other potentially pathogenic agents may evade screening. Owing to the negative insurance and other implications of diagnosing patients as HIV-positive, such material is not generally tested and it is necessary to assume some level of incidence. For autologous material, the capacity to identify individual patients with particular units of material from harvesting to reimplantation is vital. Equally, to achieve the optimal utilization of costly medical facilities and staff it will be necessary for them to be able to easily check the in-process status of material for treatment scheduling. For the regenerative medicine sector to progress from a cottage industry to a mature one, all these developments must take place within a framework of agreed international standards. Russell has suggested recently that scientific journals in the field of regenerative medicine should insist on minimal data standards and methodologies [37]. This would be a valuable complement to equipment, software and manufacturing standards. Although these challenges may appear large, it is notable that the difficulties of establishing production of therapeutic proteins were similarly great at a comparable stage 20 years ago, but very demanding operations, such as culture above 10 m<sup>3</sup> bioreactor scale, are now becoming well established.

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**Bibliography**

1. Bohmer RM: Medicine's service challenge: blending custom and standard care. *Health Care Manage. Rev.* 30, 322–330 (2005).
2. Mason C, Hoare M: Regenerative medicine bioprocessing: building a conceptual framework based on early studies. *Tissue Eng.* (In press) (2006).
3. Nyul LG, Udupa JK, Zhang X: New variants of a method of MRI scale standardization. *IEEE Trans. Med. Imaging* 19, 143–150 (2000).
4. Dekker L, Douros I, Buxton BF, Treleaven P: *Second International Conference on 3-D Imaging and Modelling* (3DIM '99) 388 (1999).
5. Pitta DA: Marketing one-to-one and its dependence of knowledge discovery in databases. *J. Consumer Marketing* 468 (1998).
6. Hagyard P, Spooner NR, Marriott R: *Intelligent Information Systems, 1996 10 Australian and New Zealand conference.* Adelaide, South Australia, 18–20 November 1996.
7. Williams TG, Rowland JJ, Lee MH, Neal MJ: *Proceeding of the 2000 IEEE International Conference on Robotics & Automation.* San Francisco CA, USA, 24–28 April 2000.
8. Dunnill P: The future of biotechnology. *Biochem. Soc. Symp.* 48, 9–23 (1983).
9. Tomar R: Total laboratory automation and diagnostic immunology. *Clin. Diagn. Lab. Immunol.* 6, 293 (1999).
10. Conn RB, Snyder JW: Changes in the American health care system: crisis in the clinical laboratory. *Clin. Chim. Acta* 267, 33 (1997).
11. May S: Strategies for medium-throughput automated genotyping methods. *Psychiatr. Genet.* 12, 127–132 (2002).
12. Mehrabi MG, Ulsoy AG, Koren Y: Reconfigurable manufacturing systems: key to future manufacturing. *J. Intelligent Manufacturing* 11, 403 (2000).
13. Magee MJ, Mack MJ: Robotics and coronary artery surgery. *Curr. Opin. Cardiol.* 17, 602–607 (2002).
14. Louw DF, Fielding T, McBeth PB, Gregoris D, Newhook P, Sutherland GR: Surgical robotics: a review and neurosurgical prototype development. *Neurosurgery* 54, 525–537 (2004).
15. Karkkainen M: Increasing efficiency in the supply chain for short shelf life goods using RFID tagging. *Int. J. Retail Distrib. Manage.* 31, 529 (2003).
16. Harrop P: *IHM Annual Conference.* Scottish Exhibition and Conference Centre Glasgow. Institute of Healthcare Management. Published Atalink Ltd, UK (2004).
17. Roberti M: Navy reves up RFID sensors. *RFID J.* (2004).
18. Padley D, Koontz F, Trigg ME, Gingrich R, Strauss RG: Bacterial contamination rates following processing of bone marrow and peripheral blood progenitor cell preparations. *Transfusion* 36, 53–56 (1996).
19. Prince HM, Page SR, Keating A *et al.*: Microbial contamination of harvested bone marrow and peripheral blood. *Bone Marrow Transplant.* 15, 87–91 (1995).
20. Schwella N, Rick O, Heuft HG *et al.*: Bacterial contamination of autologous bone marrow: reinfusion of culture-positive grafts does not result in clinical sequelae during the posttransplantation course. *Vox Sang.* 74, 88 (1998).
21. Webb IJ, Coral FS, Andersen JW *et al.*: Sources and sequelae of bacterial contamination of hematopoietic stem cell components: implications for the safety of hematotherapy and graft engineering. *Transfusion* 36, 782–788 (1996).
22. Phinney DG, Kopen G, Righter W, Webster S, Tremain N, Prockop DJ: Donor variation in the growth properties and osteogenic potential of human marrow stromal cells. *J. Cell. Biochem.* 75, 424–436 (1999).
23. Matsuoka H, Komazaki T, Mukai Y *et al.*: High throughput easy microinjection with a single-cell manipulation supporting robot. *J. Biotechnol.* 116, 185 (2005).
24. Wang MM, Tu E, Raymond DE *et al.*: Microfluidic sorting of mammalian cells by optical force switching. *Nat. Biotechnol.* 23, 83–87 (2005).
25. Ruiz-Torres A, Gimeno A, Melon J, Mendez L, Munoz FJ, Macia M: Age-related loss of proliferative activity of human vascular smooth muscle cells in culture. *Mech. Ageing Dev.* 110, 49–55 (1999).
26. Stenderup K, Justesen J, Clausen C, Kassem M: Aging is associated with decreased maximal life span and accelerated senescence of bone marrow stromal cells. *Bone* 33, 919–926 (2003).
27. Haddad H, Windgassen D, Ramsborg CG, Paredes CJ, Papoutsakis ET: Molecular understanding of oxygen-tension and patient-variability effects on *ex vivo* expanded T cells. *Biotechnol. Bioeng.* 87, 437–450 (2004).
28. Anon: Human cells, tissue, and cellular tissue-based: donor screening and testing and related labelling. Department of Health and Human Services Food and Drug Administration. *Fed. Regist.* 70, 29949–29952 (2005).
29. Preti RA: Bringing safe and effective cell therapies to the bedside. *Nat. Biotechnol.* 23, 801–804 (2005).
30. Anon Code of federal regulations, food and drugs administration Title 21, CRF part 11, "Electronic records; electronic signatures": US Government Printing Office. *Fed. Regist.* 62(54), 13429–13466 (1999)
31. Anon: Code of federal regulations, food and drug administration Title 21 CRF part 1271. Human cells, tissue and cellular tissue based products: establishment registration and listing: final rule: US Government Printing Office. *Fed. Regist.* 68(13), 2689–29952 (2001)
32. Kino-Oka M, Ogawa N, Umegaki R, Taya M: Bioreactor design for successive culture of anchorage-dependent cells operated in an automated manner. *Tissue Eng.* 11, 535–545 (2005).
33. Coury HJC, Leo JA, Kumar S: Effects of progressive levels of industrial automation on force and repetitive movements of the writ. *Int. J. Indust. Ergonomics* 25, 587 (2000).
34. Naughton GK: From lab bench to market: critical issues in tissue engineering. *Ann. NY Acad. Sci.* 961, 372–385 (2002).
35. Archer R, Wood L: Production tissue culture by Roberts. In: *Animal Cell Technology: Developments, Processes and Products* (11th ESACT annual meeting). Spier RE *et al.* (Eds.). Butterworth Heinemann 402 (1992).
36. Xu J, Ge H, Zhou X, Yang D: Tissue engineering scheming by artificial intelligence. *Int. J. Art. Organs* 28, 74–78 (2005).
37. Russell AT: Standardized experimental procedures in tissue engineering: cure or curse? *Tissue Eng.* 11, vii (2005).

**Patent**

101. ROOS E, O'REILLY C, CHEVERE R, WILKINS LM: Culture dish and bioreactor system: US6730510 (2004).