EDITORIAL

Cell & Gene Therapy, and Regenerative Medicine – Different Definitions

Chris Mason, Elisa Manzotti & Emily Culme-Seymour

> "Equating regenerative medicine, and cell and gene therapy is highly confusing and does both a major disservice...due to the increasing divergence, extraordinary attempts are now required to maintain the fiction. "

The scientific and clinical ancestry of today's cell and gene therapy sector can be traced back centuries. The first blood transfusion at Guy's Hospital London in the early 19th century may well have been the start [1]. Transfusion and organ transplantation have transformed the lives of millions of patients; however, they have their short-falls including limited supply, variable consistency, immunological rejection, potential for pathogenicity, and high cost. Thus out of necessity, two potential solutions emerged: tissue engineering and xenotransplantation. During the 1980s and 1990s, tissue engineering progressed rapidly in the laboratory, but proved near impossible to translate into routine clinical practice despite billions of dollars of investment. During the same time, xenograft technology underwent a similar fate with progress stalling due to a combination of concerns over porcine endogenous retroviruses and major immunology hurdles. The early 2000s were an all-time low for tissue engineering and xenograft technology in part due to the knock-on effects of the dot-com bubble bursting, but principally due to the excessive hype, cost and unrealistic time-lines. At the same time, gene therapy was also at its all-time low due to unexpected clinical events including the death of Jesse Gelsinger and a number of cases of leukemia caused by insertional mutagenesis [2,3]. Public support and funding went from a record high in 2000 and 2001 to

almost nothing. The science was just too early to deliver on the hype. The tissue engineers, xenograft proponents and gene therapists all passionately continued to believe that their technologies would one day be ready for prime time. The pragmatic solution for the sector was to loosely rebrand under the regenerative medicine 'flag of convenience'. Albeit it far from accurate for the vast majority of the approaches, it enabled much needed finance, public support and most importantly, a route forward. Governments, states and investors across the world embraced the rebranded sector and the billions of dollars flowed back in again, for example the $3B California Institute for Regenerative Medicine (CIRM). Over the past decade, gene therapy, and more recently gene editing, have been transforming tissue engineering, xenograft technology, and cell and stem cell therapy. *In vivo* gene therapy has likewise started to come good, for example the late-stage clinical trials for hemophilia. The tide has turned, but unfortunately, the label "regenerative medicine" has stuck, to the detriment of both real regenerative medicine, and cell and gene therapy. Now is therefore the time to make the necessary correction.

The term "regenerative medicine" first appears to have used in a 1992 paper by Dr Leland Kaiser [4]. Under the heading, "Regenerative Medicine" he proposed, "a new branch of medicine will develop that attempts to change the course of chronic disease and in many instances will regenerate tired and failing organs" [4]. Kaiser is very clear in his intent for the new medical speciality; however, over the following 30 years the term has been corrupted mainly for political and commercial gains, to be the populist term for a number of platform technologies including initially tissue engineering [5], then cell therapy, and more recently cell and gene therapy. Whilst it may have generated some short-term gains, the incorrect use of this nomenclature in the longer term has been increasingly misleading and unhelpful. To address the inconsistency, definitions for the term "regenerative medicine" have been proposed by a number of academics [6–8] and can be summarized as: "regenerative medicine replaces or regenerates human cells, tissue or organs, to restore or establish normal function" [9]. Whilst cell and gene therapy, and regenerative medicine do have overlaps, they are two very distinct and different entities. Regenerative medicine is akin to a medical specialty, and as such can be performed using any combination of approaches taken from all four pillars of healthcare; small molecule drugs, biologics, biomaterials and devices, and cell and gene therapy [10]. In contrast, cell and gene therapy is the therapeutic application of cells or genetic material to modify a patient's cells (*in vivo* or *ex vivo*). Since this is, therefore, a platform technology, it is independent of any specific medical indication. Whilst some cell and gene therapies are regenerative in their mechanism of action, for example Holoclar™ (Chiesi, IT; corneal epithelium regeneration using adult stem cells), the vast majority are not. This division is growing, with regenerative medicine, and cell and gene therapy rapidly diverging in both medical indications and approaches. For example, the pharmacology of regenerative medicine is starting to evolve [11], enabling "pharmacological science to accelerate, optimize,

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and characterize (either *in vitro* or *in vivo*) the development, maturation, and function of bioengineered and regenerating tissues" [12]. Cell and gene therapy is increasingly expanding its boundaries including oncology, mono-genetic disease and immunology applications, with regulatory-approved products available, for example UniQure's Glybera® (*ex vivo* gene therapy for lipoprotein lipase deficiency), and GSK's Strimvelis™ (*ex vivo* gene therapy for adenosine deaminase-severe combined immunodeficiency syndrome [ADA-SCID]), and thousands of non-regenerative clinical trials underway.

Both regenerative medicine, and cell and gene therapy have major opportunities to tackle unmet medical needs as well as degenerative diseases, which are an increasing challenge for aging societies [13]. However, their approaches in the main will be independent and thus each has different challenges and obstacles to overcome. Equating regenerative medicine, and cell and gene therapy is therefore, highly confusing and does both a major disservice. For example, due to the increasing divergence, extraordinary attempts are now required to maintain the fiction. This confuses everyone; politicians, policy makers, funding agencies, investors, patients and the public. An example of where this confusion is maximally unhelpful is cost-effective scalable manufacturing. This is repeatedly flagged as a major bottleneck for the advancement of regenerative medicine [14,15], but is a major distortion of the truth. For decades the big pharmaceutical companies and biotechs have successfully manufactured small and macromolecule drugs with increasing success. Thus regenerative macromolecule drugs, for example erythropoeitin (recombinant hormone that stimulates red blood cell production), are routinely manufactured generating billions of dollars in revenues every year. The real issue at hand is the need to successfully manufacture cell and gene therapies at scale, since bioprocess investment, infrastructure and innovation currently lag many years behind product innovation. Similar disparities in challenges between regenerative medicine, and cell and gene therapy occur throughout the translation cycle including regulation, clinical trials, reimbursement, supply chains, cost of goods, and business models – issues which are all well understood with respect to medical devices, and small and macromolecule drugs, but are still in their infancy with respect to cell and gene therapy.

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Regenerative medicine, and cell and gene therapy are not interchangeable terms, but both will be highly important in the future of medicine and human health. Regeneration is regeneration, period. Why should it be anything else? The term does not need to be somehow twisted to include the massive depth and breadth of applications potentially possible with cell and gene therapy. Likewise, much of regeneration is likely to be through the combination

of multiple therapeutic modalities including small- and macro-molecular drugs [16], materials, and devices as well as, where appropriate, cell and gene therapies. There will therefore be some overlap. The goal of regenerative medicine is to disruptively transform the current inevitability of aging and degeneration, and disability through trauma – unmet medical needs for everyone. Predicting the future of cell and gene therapy is nigh on impossible since the technology is so early in its development. Early wins are to be able to produce durable patient outcomes, and even curative responses, and in many cases replacing palliative therapies and symptom management, and what will be seen as the old paradigm of a 'pill-a-day-for-life'. The massive potentials of cell and gene therapy, and regenerative medicine will not be realized for decades; their impacts will be different but both will be game changing. It is therefore long overdue that we lower the regenerative medicine flag of convenience once and for all.

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AFFILIATIONS

Chris Mason
Chief Science Officer,
AvroBio Inc., 400 Technology Square
Cambridge, MA 02139, USA
&
Professor of Regenerative Medicine Bioprocessing, Advanced Centre for Biochemical Engineering, University College London, Bernard Katz Building, Gordon Street, London WC1H 0AH, UK

Elisa Manzotti
CEO and Founder, BioInsights
e.manzotti@insights.bio

Emily Culme-Seymour
Gene Therapy, Rare Diseases Unit, GSK, 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK

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