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Bridging Regenerative Medicine Based Therapies into the 21st Century: Solo or Symphony?

REVIEW

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Abstract

Clinical translation in the field of regenerative medicine means manufacturing a safe, reproducible and effective clinical product for the benefit of patients. This represents the ultimate goal of applied research, but beyond researchers and clinicians, multiple intermediate players are involved, including other researchers, reviewers, funding agencies, scientific societies, guideline authors, and policy regulators. Consequently, bridging translational research and regenerative medicine therapies into the 21st Century requires a resolute effort. We envisage that strategic and synergistic efforts in seven key areas will facilitate the mainstream adoption and implementation of regenerative medicine based therapies.

Keywords
Basic research; cardiovascular disease; outcome research; translational research

Background

Nowadays biomedical research focused on regenerative medicine therapies is afflicted more than ever by an awkward paradox: several apparently striking discoveries turn out to be utterly non influential in the setting of real-world point of care of our patients. Specifically, we are faced with a plethora of small or moderately-sized trials of different quality, sometimes challenging each other and often not able to generate robust scientific evidence with an immediate impact on healthcare. The result is that researchers, clinicians and also patients are pushed in different directions, and such dissimilar effect estimates highlight mixed results with benefits ranging from absent to transient or, at most, marginal [1].

Clinical translation, which means a safe, reproducible and effective clinical product/protocol for the benefit of patients, is the ultimate goal of applied research, but beyond researchers and clinicians, multiple intermediate players are involved, including other

researchers, reviewers, funding agencies, scientific societies, guideline authors, and policy regulators. However, to date, the mainstay of the entire field has largely been the extended and often exceedingly liberal use of small-sized clinical trials, as well as the dispersion in preclinical or clinical research due to poor assessment of the value of analytical methods –e.g., factorial designs, large simple studies, and longer-term follow-up of completed studies– which might have low incremental cost compared to the information yield. Probably lower costs and stronger results could arise from better allocation of available resources, from more intense exploitation of systematic reviews to select high-priority scientific questions and from better study design and interpretation of final results.

How can biomedical research adapt and cope with this challenging scenario in order to produce solid and informative data to answer and possibly solve, at least in part, the problems burdening society and individuals? And how could biomedical research become easily available and not exclusively reserved to developed countries? We believe that these simple questions hold the entire heart of the matter.

More poignantly, bridging regenerative medicine therapies ahead requires a resolute effort. We envisage that strategic and synergistic efforts in seven key areas may strongly facilitate the mainstream adoption and implementation of regenerative medicine based therapies. These areas include: (1) the field of regenerative medicine, (2) public-private partnerships, (3) improved regulatory standards, (4) advanced manufacturing systems, (5) extensive networking, (6) integrated databases and (7) widespread banking.

Discussion

Field of action of regenerative medicine

The real biological potential of many stem cell types seems the main limiting issue to the development of proper cell-based strategies intended for regenerative medicine. Hence, the first step should be a rigorous and thorough redefinition of the anatomy, nature, identity, location, phenotype and potency of non-embryonic progenitor cells. Recently, the extremely liberal use of stem cells (adopted both, as a biological concept, as well as the most popular tool in regenerative medicine) represents one of the key difficulties of cell-based regenerative approaches. For example, MSCs (precursors of bone, cartilage, fat and fibroblasts) have been almost universally regarded as a ubiquitous cell type endowed with a broad, even unrestricted potency. A canonical line in the introduction of virtually every paper in the field evokes their widely assumed, and yet never rigorously proven, ability to generate a number of other nonskeletal mesoderm derivatives, such as muscle or endothelial cells, and even a number of non-mesodermal cell types, such as neurons or liver cells. Many of the events depicted in vitro (clonal growth) and in vivo (differentiation toward cartilage or muscle, assembly of blood vessels, recruitment of mesodermal progenitors to a microvascular niche, pattern formation) not always correspond to real therapeutic benefits after clinical translation, with results ranging from absent to marginal. In reality the scientific community is remote from solving this Gordian knot, since more fundamental biological questions arisen from pre-clinical animal models (cells interaction or coupling with other cells, grow, differentiation, creation of patterns, real tissue generation, paracrine effects, apoptosis) still have to be fully addressed in order to overturn events defined as "stochastics" and yet, in essence, not understood into unquestionable.

Public-private partnerships

Building a solid cooperative relationship between public entities, such as state universities and private institutions and companies, by means of incentives for public-private partnerships to advance regene-

rative medicine, is unquestionably paramount [2]. Right now, ''Horizon 2020'' has to be seen as an opportunity to chase a common and structured research policy at European level,

strengthening existing programs and generating new ones within academia and industry by accommodating established partnerships between universities and industry. Consistent with ''Horizon 2020'', these types of partnership bring together the very best leaders and innovators in the field, who have the collective expertise to translate basic science discoveries into clinically and commercially available products. No single individual, nor any single company/institution alone could likely be as proficient in performing this task. This can be appreciated also by comparing countries with only a national public health system to those with private healthcare or hybrid systems: public universities and governments alone are most likely unable to support the development 'from bench to bedside' of advanced, expensive and experimental treatments, while private investors and interests are often useful to reach market scale of biotechnological products. Becoming aware of this premise is a critical step toward the adoption of a new research model suitable for real translational success. These formed partnerships or consortia will ensure the momentous advantages of: creating mutual resources; integrating expertise from different disciplines toward the same objective; developing pre-competitive spaces for development of high-risk innovative technologies; teaching students and scholars; harmonizing technology transfer by creating master research agreements to facilitate collaboration and avoid common hurdles around patenting and intellectual property; developing highly-qualified expertise that can be used by consortium members to foster their own internal research efforts; creating access to shared facilities (e.g. clean rooms and Good Manufacturing Practices [GMP] suites), as well as numerous other benefits. In few words, this will help bridging the gap between education, translational research and real-world point of care medicine.

Regulatory standards

A second challenge is to address the complexity of regenerative medicine therapies within an adequate regulatory frame able to transfer innovation into clinical practice in a controlled and safe situation, protecting patients and allowing better healthcare at the same time. To achieve the clinical translation of any pharmaceutical, medical, or biotechnological product, the development of well-defined conditions for production, processing, and culture is required at every level. Clinical translation demands compliance with current GMPs for the optimization of cell preparation following specific protocols, such as avoidance of any xenogenic animal product or granting adequate quality standards confirmed by detailed protocols [3, 4, 5]. International guidelines and agreements establish that pharmaceutical and medical device companies must comply with GMP criteria, and should conform their own quality standards to duly uniform themselves with the corresponding legislation. Stem cells are defined as 'advanced therapy products', and must be handled and manipulated under GMP approved protocols, analogously to active pharmaceutical products (see Eudralex EU guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use), otherwise to be considered 'outlaw'. Therefore, full compliance with GMP is a mandatory aspect of stem cell-tissue engineering and manufacturing. Within the above mentioned consortia strategies, we envision a rigorous effort to encourage regulatory partners to develop standards to make the regulatory process more efficient. Selection and optimization of the best performing protocols still need to be carried out, and developing common references that are accepted by regulators for stem cells or different tissue-engineered and regenerative medicine-based products, will enable companies to have a more systematic,

as well as efficient process for moving a product forward in the clinical translation process. Companies which engage in developing these regulatory standards will have enormous benefits by recommending which sets of guidance should be used by the entire field (including standards used by their competitors) to determine safety, efficacy and traceability in compliance with GMP guidelines. Regulators will also be able to address concerns and key issues with different products by early identifying common challenges and ensuring proper standards to be developed, and to enable safe and efficient translation of stem cell-based products into clinical practice without any sort of inference [6]. These strategies, once accomplished at the preclinical stage, could reduce costs and advance safer and more effective products forward for phase I clinical trials.

Advanced manufacturing systems

In addition to an improvement in regulatory standards, there is a need in the regenerative medicine field to incorporate advanced manufacturing setups early on in the development of stem cell and tissue engineering-based technologies. Scaling-up to "large volumes" often generates profuse technical difficulties, resulting in intensive and time consuming research efforts. This clearly represents a restraining factor hampering the final step towards clinical translation for cost-effective therapies, holding back their application into common medical practice. Specifically one of these challenges is the affordable scale-up of stem cell-based therapies. Shifting from personal/custom-made production to continuous or semi-continuous processing, is beyond a doubt a tricky challenge. Public-private partnerships, combined with government-funded incentives, are needed to develop more automated manufacturing suites that align with 21st Century technology. State-of-the-art manufacturing laboratories for allogeneic and autologous cell therapy that are based on disposable, closed, and automated manufacturing processes, are already available as prototypes, albeit at very high prices, still prohibitive for most research groups and clinics worldwide. Moreover, in order to provide stock biological products compatible with the clinical translation of heterologous stem cell therapy, development of protocols for GMP clinical-grade banking systems might generate readily available off-the-shelf products at lower costs.

Networking

Most likely, no single company/institution could be so complete and skilled in performing all the above mentioned tasks without a well-structured collaborative network. Building a supportive system for sharing information and services among public and private groups having a common objective is mandatory in the setting of biomedical and regenerative medicine research, as well as in the development of standardized protocols to be translated into clinical practice. Networking represents a problem-solving approach to the structural weakness of the solo approach. A close involvement of all the actors involved in translational research is not only capable of improving the efficiency of the entire procedure, but can also prove to be cost-effective. Capitalizing the specific expertise of several groups active in this field sharing specific skills and abilities such as technological (tailoring of nanostructures of biopolymers for scaffold functionalization, or of inorganic phases, or of nanofibers) and scientific tools, will allow not only transferable products, but ways of manipulating cells and tissues, their shapes, their structure. Networking thus represents the foreword to lay the foundations for the next area: the creation of integrated databases.

Integrated databases

Further important considerations will have to be about the development of integrated databases toward the concept of personalized, but also "collective" medicine. We blindly trust in the creation

of cloud-based databases combining numerous health records and data to assist with patient care, research, and clinical trials. Pursuit of personalized medicine protocols aims for products specificity and dosage designed for a particular individual. Fully applied, it would require complete information about the single patient, including his/her peculiar responsiveness to the treatment. Data storage in dedicated databases could allow patients matching and enrolling in a specific trial, titration to the desired therapeutic effect and potential reduction of undesired side-effects. Moreover his/her data might be available for the entire community. One might conceive the following future scenario: at birth a patient could have his/her blood/tissue banked, which in turn could be screened for disease markers, and afterwards, if needed, exploited for the development of a stem cell-based autologous and/or heterologous therapy. A patient eligible for all inclusion criteria for a specific clinical trial, could be potentially enrolled in such study. Moreover this modernized, yet pragmatic joint management, could open new frontiers with the implication that 'medications' may have greater efficacy if administered before the onset of symptoms. In addition, a drug screen panel, based on induced-pluripotent stem cell (iPSC)-in vitro-data, could be used to guide the referring physician in the choice of the best medication, as well as on the responsiveness for a customized dose. All this information, however, would have to be stored in an integrated database to be used with the proper oversight by researchers and clinicians, to have a more comprehensive and personalized approach towards medicine.

Banking

Stem cell and tissue engineering based-therapies are not always suitable for emergency scenarios. In the setting of acute diseases, such as myocardial infarction, manufacturing protocols may require days or even weeks in order to yield the appropriate number of cells able to exert their functional benefit. Thus, development of protocols for clinical-grade banking systems might generate fully-available off-the shelf products for the clinical translation of cell therapy in acute settings as well. Yet, a tricky challenge in the setting of public biobanking is represented by the high costs imputable to the creation and maintenance of these facilities [7, 8] also because regenerative medicine applications for different tissues, organs and diseases, require different stem cells and possibly different banking facilities.

Hence, the obstacle of high cost facing the establishment of public stem cell banks has prevented more than a handful from opening or operating regularly. Considering that in an ideal world, public banks should not levy storage fees, many medical centers miss the funds required to establish and maintain them. In this scenario, as previously highlighted, a tight collaboration between public institutions and private companies could represent the right direction to move forward in order to resolve this last challenge.

Summary

We believe that these seven ambitions, if actually fulfilled, will truly enable stem cell and tissue engineering-based technologies to be easily translated into clinical practice and integrated as the music of a gorgeous symphony. While implementing them effectively and in a timely fashion will be a challenge, the possible rewards can be remarkable. Regenerative medicine should start from a clinical core which is made of observations, concept and tools, and aim at wedding stem cell biology with advanced manufacturing systems, moving from insight to in-sight, and back. Only in this way stem cell and tissue engineering-based therapies have the potential for large-scale applications by healthcare systems, also possibly helping emerging countries to fill their gap with industrialized na-

tions. Many reasons could explain why different research areas are much more implemented in some countries compared to others. We could speculate considering two main variables: the social environment combined with the cultural evolution of the scientific knowledge, but also the politic asset. Particularly, frequent political changes within the government class can develop instability, resulting in continuous and different regulations sometimes even self-contradictory, thus affecting the quality of the national legislation. We have also to consider that the global economic crisis is altering the whole scenario, allowing some developing countries to became the new entrepreneurs of the 21th century.

Given the current and predicted impact of several chronic and degenerative diseases in the general population, regenerative medicine will provide the possibility to cure diseases, prolong and improve quality of life, promote economic stimulus, and even reduce the cost of medical cares. In few words, it would truly provide what we have so long sought: a Prometheus of modern times.

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Conflicts of interest
Prof. G. Frati holds a patent concerning stem cells in cardiovascular medicine (Patent Italy-RM2003A000376 31.07.2003 - WO2005012510, 2005-02-10 ,Method for the isolation and expansion of cardiac stem cells from biopsy, Owner: Sapienza University of Rome). Profs. G. Frati and L. Frati hold a patent concerning platelet lysate in regenerative medicine (Patent Italy-RM2011A000500-23.09.2011-IT-Platelet lysate, uses and method for the preparation thereof-Lysat de plaquettes, ses utilisations et son procédé de préparation, Applicants: Sapienza University of Rome [it/it]; (it). Futura Stem Cells sa [ch/ch]; (ch) Pub. No.: WO/2013/042095, International Application No.: PCT/IB2012/055062).

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Authors' contributions
GF conceived the manuscript.

All authors have been involved in drafting the manuscript or revising it critically for important intellectual content and have given final approval of the version to be published.

All authors read and approved the final manuscript.

References

1. Nowbar AN, Mielewczik M, Karavassilis M, Dehbi HM, Shun-Shin MJ, Jones S, Howard JP, Cole GD, Francis DP; DAMASCENE writing group. Discrepancies in autologous bone marrow stem cell trials and enhancement of ejection fraction (DAMASCENE): weighted regression and meta-analysis. BMJ. 2014 Apr 28; 348: g2688. doi: 10.1136/bmj.g2688. Review
2. Gaspar R, Aksu B, Cuine A, Danhof M, Takac MJ, Linden HH, Link A, Muchitsch EM, Wilson CG, Ohrngren P, Dencker L. Towards a European strategy for medicines research (2014-2020): The EUFEPS position paper on Horizon 2020. Eur J Pharm Sci. 2012 Dec 18; 47(5): 979-87. doi: 10.1016/j.ejps. 2012.09.020.
3. Fabrizi C, Angelini F, Chimenti I, Pompili E, Somma F, Gaetani R, Messina E, Fumagalli L, Giacomello A, Frati G. Thrombin and thrombin-derived peptides promote proliferation of cardiac progenitor cells in the form of cardiospheres without affecting their differentiation potential. J Biol Regul Homeost Agents. 2011 Apr-Jun; 25(2 Suppl): S43-51
4. Chimenti I, Gaetani R, Forte E, Angelini F, De Falco E, Zoccai GB, Messina E, Frati G, Giacomello A. Serum and supplement optimization for EU GMP-compliance in cardiospheres cell culture. J Cell Mol Med. 2014 Apr; 18(4): 624-34. doi: 10.1111/jcmm.12210
5. Siciliano C, Ibrahim M, Scafetta G, Napoletano C, Mangino G, Pierelli L, Frati G, De Falco E Optimization of the isolation and expansion method of human mediastinal-adipose tissue derived mesenchymal stem cells with virally inactivated GMP-grade platelet lysate.. Cytotechnology. 2015 Jan; 67(1): 165-74. doi: 10.1007/s10616-013-9667-y
6. Frati P, Frati G, Gulino M, Montanari Vergallo G, Di Luca A, Fineschi V. Stem cell therapy: from evidence-based medicine to emotion-based medicine? The long Italian way for a scientific regulation. Stem Cell Res Ther. 2013 Oct 11; 4(5): 122. doi: 10.1186/scrt333.
7. Rham C, Villard J. Potential and limitation of HLA-based banking of human pluripotent stem cells for cell therapy. J Immunol Res. 2014; 2014: 518135. doi: 10.1155/2014/518135.
8. Webb S. Banking on cord blood stem cells. Nat Biotechnol. 2013 Jul; 31(7): 585-8.