

TOWARDS A CONSTRUCTIVE DEBATE AND COLLABORATIVE EFFORTS TO RESOLVE CURRENT CHALLENGES IN THE DELIVERY OF NOVEL CELL BASED THERAPEUTIC STRATEGIES

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Soon after the Cell Transplant Society (CTS) was formed in 1991, with E. Donnall Thomas, Thomas E. Starzl and Paul E. Lacy serving as Honorary Presidents, we were worried at that time of CTS first congress (1992) about the potential risk of overregulation by FDA of the emerging field of cellular therapies.

I was told how many of the breakthroughs of the past century including bone marrow transplantation and liver transplantation could not have been possible under the current FDA rule and that the fortune of bone marrow transplantation and liver or organ transplantation in general, as well as of the patients who have benefited from these procedures, has been indeed to be able to remain out of such rule. A recent article by Scott Gottlieb, former deputy director of FDA, "How The FDA Can Cost You Your Life" (Wall Street Journal, October 3rd 2011) highlights some of these concerns in the area of devices, but many of the same considerations could apply to cellular therapies. The same day this article was published, the keynote address by Andrew Grove at the World Stem Cell Summit in Pasadena, CA, outlined how the problem started when Congress allowed FDA to extend their regulatory oversight to "efficacy" beyond "safety" (1962). If the only consideration or performance indicator is safety and risk avoidance without considering other factors, such as the morbidity and mortality of a disease condition, the resulting course of action could be doing nothing, or imposing years of additional "efficacy" demonstrations for the proposed strategy, in experimental model systems which could often reveal themselves irrelevant to the clinical setting in which an actual human cell product will be eventually used.

I am honored to have been able to serve as chairperson of the steering committee of the NIH Clinical Islet Transplant Consortium, which just completed the first Phase III trial towards registration of the first metabolically active cell product in the US. I am also proud to have served on the FDA Biologic Modifiers Committee and I am proud to have directed one of the first cGMP human cell processing facilities in

the US that was approved by FDA to ship cell products across state barriers and that is now one of 4 cGMPs in the US certified for processing more than minimally-manipulated human cell products. However, I am also deeply concerned by the cost and time requirements for any clinical trial to move forward, for many reasons including immediately life threatening conditions for which an alternative effective treatment does not exist.

In this editorial I am expressing my personal opinion and not that of NIH or the CIT consortium, but I believe that dialogue and understanding each other positions (tolerance if you wish) could be a starting point towards a much needed "resetting" of the regulatory environment for cellular therapies, to allow and promote innovative trials while maintaining the centrality of patient safety. Mandatory reporting and monitoring/audits by DSMBs will then continue to assess efficacy and safety. The introduction of "efficacy" in the definition of compassionate use is arguable as well, because if it would be efficacious (in addition to safe) shouldn't it be allowed beyond compassionate use? Just a thought ... I am happy that the debate will continue during the upcoming congress of The Cell Transplant Society, now 22 years old (<http://www.cts2013.org/>).

Clinical trials in cellular therapies have witnessed a significant growth in the number of applications targeted and patients treated, while a series of impediments and challenges on the path of translation of cell based therapies have emerged and are going well beyond patient safety concerns or risk/benefit considerations. Some regulatory environments have been largely unprepared to address such challenges, often limiting innovation and the development of new treatments.

An increasing number of scientists, clinician, patients and patient advocates are expressing concerns on whether an excess of caution from regulators may result in unacceptable delays or even completely pre-

venting the development of selected cell, stem cells and reprogrammed cells therapies from reaching patients.

Comments made by John Gurdon after winning this year's Nobel Prize in Physiology and Medicine are clearly pointing to these growing concerns: "I think patients would be happy to take the risk of using their own cells given the choice," Gurdon told a press conference in London, criticising the US Food and Drug Administration for placing "immense conditions on approval" (*Aldhous, P. and A. Coghlan, Medicine Nobel: good choice, but will cures come soon?, in New Scientists. 2012, Reed Business Information Ltd.*).

The costs related to health care delivery are becoming unsustainable, while the prevalence of chronic degenerative disease conditions is dramatically increasing. Paradoxically, also the costs and time imposed to reach regulatory approval for a new therapeutic strategy, a new molecular entity or cell based product have dramatically increased in recent decades and now even minimally manipulated, autologous cell products face the possibility to become regulated as drugs in several countries.

As an opening editorial, I would like to raise some concerns for the polarizing and highly emotional debate which is now dividing the scientific community regarding regulatory environment, translational strategies, compassionate release, safety vs. efficacy preclinical data that should be required before allowing pilot clinical testing and reimbursement issues, to name a few.

We therefore decided to dedicate a significant space in the next issues of CellR⁴ to invited as well as submitted, unsolicited papers/letters/commentaries expressing different points of view both from the scientific community, ethical, legal experts and from patients/patient advocacy groups, to discuss in a constructive and productive way the elements that could be of assistance to better understanding existing concerns and help us develop a team effort to better resolve current impediments and obstacles on the path to cures, while preserving patient safety and risk-benefit ratios, which should remain central to all efforts considered.

Below I outlined selected topics, issues and controversies that have been raised in recent months, by different editorials, articles, blogs and meetings. Since commentaries have been accepted in very selective way by some journals, for reasons that are not apparent, we believe it is important to offer an opportunity to voice opposing views and different

opinions, with the objective to provide a constructive forum for confrontation, discussion and resolution of current strategic differences on the path to develop novel treatment strategies and on what are the options to make them available to patients worldwide in the fastest, most efficient and safest way possible.

We would like to promote a constructive debate, where different opinions could be voiced, with a special emphasis on trying to reach a balanced and tolerant understanding of the concerns and possible solutions proposed by opposing positions, trying to avoid the arrogant and dogmatic statements that occasionally have characterized recent editorials and opinion papers.

Points and questions to be addressed by submitted papers/commentaries for the next issues of CellR⁴ include the following:

- **To what extent can the FDA regulate a physician's ability to treat a patient with that patient's own stem cells?** A growing number of physicians routinely offer treatments involving Autologous Stem Cells (ASCs) to their patients which can be performed in their offices. Autologous adult stem cells, used to treat a variety of conditions, are harvested from the patient, processed, and returned to the same patient. It is no surprise that moving ASCs from laboratories to physician offices raises complex questions of law. At first glance, the idea of the FDA regulating our own cells looks like an outrageous invasion of individual privacy and denial of personal autonomy. If patients weigh risks and benefits of medical treatments every day, why prevent them from doing so with their own cells? This question is especially compelling where a patient has few or no effective therapies, and limited or no access to experimental treatments. That a treatment may be more risky in the hands of untrained or unskilled doctors is not unique to autologous adult stem cell therapies; this problem pervades medical practice. The FDA should re-examine its HCT/P (Human Cell Therapy/Products) regulations especially as applied to physicians treating patients with their own cells. Extracting a patient's cells for subsequent reinjection undoubtedly carries risk – but so does banking one's own blood or freezing eggs for later use. Conditioning the extent of regulation on the degree of manipulation may make sense on paper but is vague and confusing in practice,

especially in the dynamic field of cellular therapies. In an age of relentless cost inflation and limited therapies for debilitating illness, it makes no sense to deprive patients of autologous therapies because their physician lacks the resources – and patients lack the time – to satisfy the pre-marketing requirements that oppress even Merck and Johnson & Johnson. The FDA is obligated to protect the public health as well as individual patients. Critical to this mission is striking the proper balance of risks and benefits, where the benefits include facilitating medical innovation. In the context of adult stem cell regulation, especially autologous cells, it is time for that risk-benefit balance to be recalibrated. (*Adapted from Mary Ann Chirba, J.D., D.Sc., M.P.H. and Alice A. Noble, J.D., M.P.H.; http://lawprofessors.typepad.com/healthlawprof_blog/2013/06/mary-ann-chirbajd-dsc-mph-and-alice-a-noble-jd-mph-our-bodies-ourcells-fda-regulation-of-autologous-ad.html#more*).

- **Should cellular therapies be regulated like drugs or medicinals and/or when should this shared regulatory pathway occur? Stem cell therapies, even autologous ones, should be regulated, but should those regulations be re-designed to fit the parties and products being regulated?** It makes no sense for the FDA to insist that a practicing physician who is treating an individual patient must conform to the same pre-marketing and manufacturing requirements that bind large-scale, commercial pharmaceutical manufacturers that produce drugs in bulk for mass distribution. Moreover, the agency should not monopolize risk-benefit calculations to the exclusion of patients who, with the counsel of their physicians, want to make their own calls about using their own cells to treat their own conditions. Preventing them from doing so is already leading many patients to assume other and perhaps greater forms of risk, such as seeking treatments in foreign clinics that may or may not be up to the task. Suing an agency is usually an uphill and often losing battle and it is doubtful that it could do much to lower regulatory hurdles. Some form of regulation is needed, but the FDA must recognize that its current HCT/P framework is ill-suited to many kinds of cellular therapies. It could revamp its HCT/P framework entirely, but that will take time. In the near term, the agency should reach beyond existing expert advisory committees and public comment sessions. It should engage in a true collaboration

with a wider group of physicians and surgeons who are already using or stand ready to use various types of autologous adult stem cell therapies, and the patients who have had or want treatment. It can also look to the guidelines of relevant organizations, such as the American Association of Blood Banks or various physician organizations. Only then can the FDA get a firm handle on what kinds of techniques and treatments present tolerable levels of risk when balanced with the need for innovation and the basic right of patients to use their own cells. After all, patients are the ones who must bear the burdens of illness, not the regulators, judges or attorneys. (*Adapted from Mary Ann Chirba, J.D., D.Sc., M.P.H. and Alice A. Noble, J.D., M.P.H.; http://lawprofessors.typepad.com/healthlawprof_blog/2013/06/mary-ann-chirbajd-dsc-mph-and-alice-a-noble-jd-mph-our-bodies-ourcells-fda-regulation-of-autologous-ad.html#more*).

- **Would the weakening of regulatory standards for propagated adult stem cell interventions greatly increase patient risk?** While most agree that changes are definitely needed at the FDA in some respects related to stem cells such as expanded compassionate use of stem cells for patients with fatal diseases and a push for more openness, some argue that the weakening of regulatory standards for propagated adult stem cell interventions would greatly increase patient risk. Should the extent of regulation be conditioned on the degree of manipulation since it is operationally (not just on paper) extremely important from a patient safety perspective and it makes sense that stem cells manipulated in different ways and to different degrees should be subject to different regulations? (*Adapted from commentary to the above article by Paul Knoepfler, UC Davis*).
- **Should smaller companies providing cell/stem cell products be subject to the same regulations as large multinational companies, or should the degree of regulation be proportional to the developmental stage of the cell product, the risk/benefit of proposed therapy and the relative patient size of the clinical trials considered?** Some argue that the law variable should not depend on the size of the entity that should be following that law and that just as small and large drug manufacturers of pill (chemical) drugs have to follow the same rules to provide data on safety and efficacy, smaller companies selling stem cell drug interventions should have to follow the same rules and laws as big compa-

nies. The argument is that doing otherwise put the growing number of patients treated by stem cell clinics (now in the thousands and growing) at great risk? On the other hand should it be considered that if the standards are defined by regulations that only large multinational companies can afford, this could severely limit innovation and development of new treatment strategies by smaller entities and academic centers?

- **Should all regulatory agencies have time limits to respond to IND applications or requests for inspection of cGMP Facilities?** There are increasing concerns for special emphasis commissions, expert groups and/or regulatory agencies that have no time limits to respond to requests for approval of an IND or a cell processing facility: a system in which there are requirements and guidelines, but no time frame for evaluation and eventual approval of applicants. Inspection and accreditation of cGMP facilities can possibly sit for years, with the facilities ready to operate but unable to do so, for an open ended delay in regulatory inspections, while a few individuals in a region may control what and who can perform cell therapies in that geographical area, opening the possibility that special interest groups could define criteria, access and development of novel treatments.
- **If a subject has a terminal disease or one for which there were no approved efficacious treatments, would it be ethical to receive and be charged for unproven stem cell treatments?** ... with the following caveats:
 1. It is safe to the best of our knowledge (<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0047559>);
 2. The patient and/or their caretakers understand that this is experimental;
 3. The price of treatment includes profit for the hospital/clinic the doctors and other researchers involved. Would there be a problem with a full disclosure like that? Why are there researchers who personally profit and otherwise benefit from ongoing research funding point their fingers at others when ignoring their own inherent conflicts?

“*Smoke and mirror*” is the title of a now famous (or infamous depending on the point of view) editorial on Nature (*Nature* 2013 April 18; 496: 269-270 doi: 10.1038/496269b) which was reported to represent the voice of the international scientific community position against a decree from the Italian Parliament, approved after media and patients’ families pressure in favor of the Stamina Foundation Onlus. The decree is now allowing for a limited time

controlled clinical trials of stem cell therapies within public hospitals, with a stringent regulatory oversight. There will be approximately 100 subjects treated, affected by genetic or orphan diseases, who will be allowed to start or continue a compassionate therapy, at no charge to the patients. The procedures will be performed with the cell line produced by Stamina at the Brescia Hospital’s GLP laboratory, where hospital’s biologists also routinely prepare bone marrow for transplant into leukemic children. For those who are not familiar with the saga surrounding the Stamina Foundation trials in Italy, selected arguments raised against Stamina and the (unedited) responses from Stamina Foundation have been included at the end of this article (Appendix).

While some scientists and physicians are concerned with the possible abuse of a potentially more permissive regulatory system, for example by for-profit entities or private clinics that may push for open-ended clinical treatments in the absence of a clear validation of the results and/or analysis or the efficacy of the proposed strategies, other scientists and physicians are concerned with the misleading and arrogant way that some arguments have been presented to the public. There are concerns that small group of scientists could selectively filter information available to the public, by controlling editorial boards or publishing anonymous editorials, while impeding commentaries of opposing views.

The surprising decision by the Italian Parliament in a way led the way to a wake up call, when actually what appeared at a first glance to be the overwhelming and almost unanimous position of some very vocal esponents of the scientific community, was blown away by the public response, including scientists in the Italian Parliament. In fact, the Italian Parliament passed virtually unanimously a decree that was approved at the House with 504 yes votes and only one no (4 abstentions) and that was also approved by the Senate with 259 yes votes, 2 no (4 abstentions). The approval of this decree that offers a limited window of opportunity for cellular therapies to be tested in some patients clearly made the public opinion voice heard, but still divides the scientific community.

While some voices proposed that science was united against this decree that was overwhelmingly approved by the Italian Parliament, opposing commentaries were blocked from publication, for no apparent reasons, but generating the misleading appearance that scientists on one side and politicians and the general public on the other side, were deeply divided on issues of cellular therapies and how to better explore potentially novel therapeutic strategies.

In the mean time Japan may also be moving towards a dramatic retooling of the country's drug authorization framework that could produce the world's fastest approval process specifically designed for regenerative medicine. This special track for cell based therapies will create a novel, separate approval channel for regenerative medicine where companies will have to demonstrate efficacy in pilot studies of as few as ten patients in one study, if the change is dramatic enough. If efficacy can be "surmised," the treatment will be approved for marketing. At that stage, the treatment could be approved for commercial use and for national insurance coverage. Following approval, there will be a post-market surveillance period of five to seven years, after which the treatment will be evaluated again for safety and efficacy. Every patient must be entered in a registry during that period. If the therapies prove inefficacious or unsafe, approval can be withdrawn. (<http://www.nature.com/nmj/journal/v19/n5/full/nm0513-510.html>).

On the other hand, concerns have been also expressed on ways in which the system could be abused by some commercial, for-profit interests, which should not be allowed to have an open ended opportunity to offer compassionate or unproven treatments without mandatory reporting and documentation of the results, without a Data Safety Monitoring Board or equivalent auditing/monitoring entity. We could indeed work collectively on a solution that could protect patient safety while allowing innovation and translational efforts to occur, avoiding any abuse of the system.

We therefore welcome your contributions to future issues of CellR⁴ on these topics as well as any other relevant scientific contribution, from original papers, reviews, case reports and letters, to opinion papers on current challenges and topics of shared strategic interest, on how to be as efficient as possible on the path to identify and deliver clinically relevant strategies to cure disease conditions now afflicting humankind.

APPENDIX

Selected Arguments Against Stamina Stromal Mesenchymal Stem Cell Trials And Responses (S) From The Stamina Foundation

- **MSC suitable for use in compassionate therapy must be produced in a GMP lab or facility.** (S) We disagree. The aim of a compassionate therapy should be to promptly treat a patient affected by a very serious disease, threatening his life or compromising his social life, for which no official or already approved cure is available. If the cells have to be produced in a GMP facility, the time necessary to develop the GMP methodology would be too long to treat such compassionate cases who, in the meantime, would be destined to die or to compromise their health to a point of no return.
- **MSC produced in a GLP lab don't guarantee to be safe.** (S) In our opinion the production in GLP is absolutely suitable, and the final cell product should be released for clinical use once is properly analyzed to guarantee: (1) Microbiological sterility and purity of the preparation, without the presence of undesired cells (hematopoietic, macrophages, etc.); (2) Characterization of the stem cells through their CDs; (3) Telomerase activity to exclude the presence of tumor cells; (4) The cells' viability; (5) DNA genetic analysis; (6) Cell number
- **Fetal Bovine Serum (FBS) does not comply with GMP and should be banned.** (S) We don't agree. FBS free media should be proven to allow to obtain the same cell products before replacing validated FBS based media.
- **The production methodology has to be fully disclosed to Authority.** (S) We don't agree. We would rather propose to supply the list of all the cultural media, the components used and the characteristics of the final cell product to be administered.
- **MSC can induce cancer.** (S) At this regard, MSC are recognized as safe cells also by EMA, while Embryonic and IPS cells are not (January 14, 2011; EMA/CAT/571134/2009; Committee for Advanced Therapies – CAT). We underline that telomerase activity is assessed on every cell line.
- **Cells could induce a rejection reaction.** (S) STAMINA stem cells do not express the HLA DR, therefore they don't need any immunosuppression of the patient. They can be used both in autologous and allogenic transplant, regardless the race and the sex of the donor and the patient. In case patient suffers from a genetic disease, the transplant should always be allogenic. In case of allogenic use, the donor should always be subject to proper analysis, similar to the ones usually performed in case of organ transplant, except for the tissue compatibility.

- **MSC cannot be useful for diseases which are so different from each other; they are not "magic".** (S) We don't agree. MSC are not chemical drugs which act by interacting with specific receptors. MSC are like a "Drug-store"; in fact they can deliver a lot of chemical substances, including proteins, enzymes, growth factors, as required. Moreover, they can substitute dead cells and help repair other cells, so performing a global regenerating effect. They can modulate the immune system, by increasing Treg and regulate various cytokines. They have also been shown to partially inactivate bacteria and viruses. Due to all such activities, it's comprehensible why they can be active and give benefits in hundreds of disease conditions.
- **MSC trials should undergo three clinical phases for each single disease indication.** (S) Due to the fact that MSCs like Stamina's have proven to be safe and that theoretically the number of rare and orphan diseases are some thousands, it is recommended that each cell preparation should only undergo clinical Phase I trials (i.e., 10-40 subjects depending on the prevalence of the disease condition) and then go directly to a Phase IV post marketing. This would save a lot of patients.

BIOGRAPHICAL SKETCH AND FINANCIAL DISCLOSURE

CAMILLO RICORDI, M.D.

Editor-in-Chief

Camillo Ricordi, M.D. is the Stacy Joy Goodman Professor of Surgery, Distinguished Professor of Medicine, Professor of Biomedical Engineering, and Microbiology and Immunology at the University of Miami (UM), Florida, where he serves as Director of the Diabetes Research Institute (DRI) and the Cell Transplant Center. Dr. Ricordi also serves as Responsible Head of the Human Cell Processing Facility, an NIH funded cGMP (current Good Manufacturing Practices) facility that has been providing Human Cell Products for research and clinical applications at UM, in Florida and worldwide since 1993.

Dr. Ricordi was president of the Cell Transplant Society (1992-94), co-founder and chairman of the National Diabetes Research Coalition (Chairman 1997), co-founder and president (1999-2001) of the International Association for Pancreas and Islet Transplantation (IPITA), and a member of the council of The Transplantation Society (2002-2008). He also served on the council of the American Society of Transplant Surgeons (2000-2002), on the National Institutes of Health (NIH-NIAID) Expert Panel on clinical approaches for tolerance induction, on the FDA Biologic Response Modifiers Advisory Committee, on the NIH/NCRR Islet Cell Resources (ICRs) Executive Committee, on the NIH-NIDDK Strategic Planning Committee and on the NIH-NIAID Expert Panel on Transplantation Research. He is currently serving as Chairperson of the Clinical Islet Transplant Consortium (NIDDK-NIAID). He has also been serving on several NIH study sections in addition to serving as a reviewer for several international funding agencies.

Dr. Ricordi has received numerous honors and awards, including the 2001 Nessim Habib World Prize in Surgery (University of Geneva) for developing a technology that significantly contributed to the advancement of a surgical field. He was awarded the 2002 Outstanding Scientific Achievement Award and delivered the Lilly Lecture at the 2002 Congress of the American Diabetes Association. He also delivered the opening plenary (Galileo Lecture) at the European Association for the Study of Diabetes (EASD) Congress in Rome (2008). In 2009 Dr. Ricordi was Knighted by the President of the Republic of Italy in the highest Order of the Republic (the Order of Merit) with the Knighthood decoration of Cavaliere Ufficiale and in 2010 he was only surgeon and one of the few ever inducted into the Association of American Physicians (AAP). In 2011 Dr. Ricordi received the D-Life's Top Award for making the biggest difference in diabetes in 2010 (international web-based public vote competition).

Dr. Ricordi is currently serving on the editorial boards of *CellR⁴* (*Editor-in Chief*), *Cell Transplantation* (Co-Editor-in-Chief) and also served on the boards of *American Journal of Transplantation* (Associate Editor), *Transplantation*, *Transplantation Proceedings*, *Tissue Engineering*, and *Graft* (Editor-in-Chief, 1998-2002).

Dr. Ricordi serves as President of the Cure Alliance (www.thecurealliance.org) and Chairman of the Diabetes Research Institute Federation (www.diabetesresearch.org), coordinating and promoting cure focused research at over 24 leading institutions worldwide, while further developing the Telescience platform technology to eliminate geographic barriers to scientific collaboration. These initiatives now allow scientists and project teams from around the world to synergize efforts and work together like if they are in the same physical space. Dr. Ricordi has authored over 700 scientific publications.

FINANCIAL DISCLOSURE. As an inventor, Dr. Ricordi has been awarded 18 patents. He was founding scientist, holds stocks/stock options and serves on the Scientific Advisory Board of several Biotechnology Companies, including Converge Biotech, Inc., Ophysio, Inc., Betagenon, Inc., Lipogems, Inc., Axelera, Inc., Betalogics Inc. and Neva Scientific, LLC. Dr. Ricordi has waived any compensation, royalty or equity for any islet cell processing technology he has developed to facilitate "open source" access to the inventions and related technologies. He has also waived editorial compensation for serving as Editor-in-Chief of *CellR⁴*, to redirect them as donations to The Cure Alliance.