OPINION

Autologous cell therapies: challenges in US FDA regulation

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Cell-based therapies (CBTs) have been hailed for the last two decades as the next pillar of healthcare, yet the clinical and commercial potential of regenerative medicine has yet to live up to the hype. While recent analysis has suggested that regenerative medicine is maturing into a multibillion dollar industry, examples of clinical and commercial success are still relatively rare [1–3]. With 30 years of laboratory and clinical efforts fueled by countless billions in public and private funding, one must contemplate why CBTs have not made a greater impact. The current regulatory environment, with its zero-risk stance, stymies clinical innovation while fueling a potentially risky medical tourism industry. Here, we highlight the challenges the US FDA faces and present talking points for an improved regulatory framework for autologous CBTs.

Clearly the FDA's risk-averse stance toward the clinical use of high-risk medical technologies has influenced the commercialization of medical innovation. While the USA still plays a prominent role in the discovery phase, today, few technologies are translated to initial clinical use through the US regulatory framework. Most CBTs, like other recent medical innovations (i.e., abdominal aortic aneurysm repair or transcatheter valve devices) are developed through an Asian- or EU-centric pathway. Geron's recent exit from the field of regenerative medicine after a US-centric strategy is attributed by most observers directly to the FDA's aggressive stance and protracted pathway to initial human testing [4]. This departure serves as a sad reminder of the negative economic and clinical impact of an ultraconservative approach, and supports such conclusions made elsewhere [5,6]. That said, the FDA is an underfunded and understaffed agency in the unenviable position of trying to regulate the best-funded and most innovative biomedical industry in the world. No one will argue that it is challenging to produce guidance documents at a rate matching the evolution of CBTs. Moreover, the FDA's conservative stance is somewhat understandable in light of the unfairly harsh press and political fallout surrounding previous failures (e.g., Vioxx, silicone breast implants) as well as societal and legal trends toward zero-risk [7–9]. This does not, however, justify a regulatory framework that stalls the clinical development of these technologies.

While it may be unfair to correlate the slow progression of CBTs solely with an overly exuberant FDA, it is clear that the regulatory framework in the USA has played a prominent role in creating a stem cell 'tourism' industry. While it is difficult to accurately assess the size of this market, we estimate that there are approximately 350 stem cell clinics worldwide seeing an average of five tourists per month, giving a total of 21,000 stem cell medical tourists each year out of a total of 3,000,000 medical tourists. Through interviews we have estimated that each treatment costs approximately US$25,000 resulting in an annual spend of over US$500 million on unregulated stem cell treatments. This represents approximately 0.7% of the overall medical tourism patient flow and about 3% of the total revenues (assuming total worldwide revenues generated by medical tourism are US$15 billion) [101,102]. It is ironic, then, that at the height of the negative press surrounding stem cell tourism, the FDA is exerting an even greater influence in attempting to redefine CBTs and cracking down on US-based clinics conducting point-of-care treatments under the practice of medicine [10–13]. The most striking of recent events is the dismissal of the lawsuit against the FDA brought by regenerative sciences [14]. This court case, in combination with a lawsuit from Cytori Inc., moves by the Texas Medical Board, and FDA warning letters sent to physicians harvesting stromal vascular fraction, have brought the situation to the forefront of both the scientific and lay press [15,103,104]. Adding to the irony is the fact that some of the most vocal and influential participants in this debate come not from a medical, scientific, or even legal background, but rather, a religious or ethical background [14,16]. It would seem that the availability of adult autologous stem cells should

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be based on rational safety and efficacy arguments, and the debate should be driven by individuals with the training and experience to appropriately evaluate the risk and benefit associated with manufacturing controls or treatment methodology.

As we analyze this situation and try to provide improved regulatory paradigms, it is important to objectively recognize the biases, shortcomings and financial incentives held by the various stakeholders. On one end of the spectrum is the academic community. Through societies such as the International Society for Stem Cell Research, this community tends to echo the FDA's conservative stance, and encourages continued bench-top and animal research. While justified in many cases, we cannot ignore the potential financial self-interest served by this message. That is, the NIH-funded academic community is well served by a regulatory policy that promotes a longer and basic research-intensive developmental path. Indeed it is no surprise to see the International Society for Stem Cell Research closely linked to the war on stem cell clinics [17,105]. With pressures from the NIH roadmap to focus on translational research, however, it will be interesting to see how this viewpoint evolves. On the other end of the spectrum are physicians delivering point-of-care therapies with autologous cells, who argue that point-of-care therapies help fuel medical innovation and can be adequately regulated by state medical boards. Here the potential conflict of interest is more evident, with enormous financial incentives tied to stem-cell treatments that can cost in excess of US $20,000. While physician-based societies such as the International Cellular Medicine Society tend to advocate clinical innovation and the delivery of therapies under the scope of the practice of medicine, this vision is sullied by images of rogue clinics that operate without regard for patient safety or benefit [106].

Industry plays an important role in this ethical and legal debate, as their (typically) allogeneic products may be threatened by autologous, point-of-care therapies. In theory, allogeneic products should be cheaper to manufacture and administer than autologous therapies. However, the extensive costs associated with FDA regulation and manufacturing oversight of mass-produced allogeneic cells may negate these theoretical cost savings. With no clear efficacy benefit for most patient populations, point-of-care, autologous therapies represent a real threat to the penetration rates most commercial entities project. This makes for strange bedfellows, as industry lobbies for tougher regulations for point-of-care therapies in an effort to create a more significant barrier to entry for autologous therapies offered by these physicians. Caught in the middle of these three competing stakeholders is the FDA, trying to balance clinical innovation with their mandate from Congress to maintain public safety.

Perhaps most importantly, we must consider this situation from the perspective of the patient. Fueled by wild promises of efficacy and fantastical images in the lay press, it is no wonder that desperate patients look to stem cell therapies for hope. With few objective tools to help guide them, the situation is primed for disappointment and potentially unnecessary health risks. Unequivocally, the situation as it exists today is a disservice to patients, and creates an economic sinkhole for the federal government. While we sink billions into federally funded research, few therapies reach the clinic to make a positive impact on public health. Meanwhile, Americans funnel hundreds of millions of dollars to offshore clinics. The real problem with point-of-care autologous therapies, however, is not the risk of communicable diseases or tumorigenesis, for example – those risks are easily mediated by reasonable manufacturing and safety measures, and generally lower than alternative therapies. Indeed it is puzzling to contemplate, for example, the FDA's concerns with tumorigenesis for stem cell treatments targeted at congestive heart failure. Given the safety and efficacy that both autologous and allogeneic stem cells have demonstrated for myocardial regeneration, it is remarkable that only a few thousand patients have been treated in the USA and EU since the first human use more than a decade ago. Meanwhile, approximately 200,000 Americans are dying every year from congestive heart failure or complications of myocardial infarction awaiting the outcome of this debate [18]. Given the lack of alternatives for these patients, it is unforgivable that CBTs have not been made more readily available. While critics understandably point to the poor risk–benefit ratio associated with less scientifically justifiable treatments, it is puzzling to see the same arguments applied to clinics performing orthopedic procedures, myocardial regeneration, lower limb angiogenesis, for example.

The fundamental problem, then, is that there are few tools by which regulators or patients can objectively measure risk–benefit. For allogeneic therapies, it is difficult to contemplate a major shift in the existing regulatory framework. While there are a variety of ways to streamline the overall review process without introducing undue risk, the FDA rightfully looks at these allogeneic products as mass-produced technologies, and puts significant manufacturing and quality assurance hurdles in place to minimize the risk of product failures that can affect thousands of patients. For autologous, point-of-care therapies, however, it is difficult to make the same argument. Despite the various perspectives, incentives and biases outlined above, there are several points that most experts would objectively agree upon:

- The restrictive FDA regulatory framework, as it exists today, is a significant driver in building 'stem cell tourism.' As opposed to developing a streamlined process for evaluating the

safety and efficacy of autologous therapies, it drives patients to clinics abroad, outside of the legal and regulatory oversight and authority inherent within the US healthcare system;

- Autologous therapies do not represent a public health risk in the same sense as a mass-produced drug, but rather, represent a risk more akin to a surgery than a drug;
- It is neither cost–effective nor feasible to expect the same manufacturing quality controls for autologous therapies as those in place for mass-produced allogeneic therapies (just as one would not expect the same quality control burden in an operating room as in a device manufacturer's clean room);
- The risks associated with the nonhomologous delivery of adult, autologous cells (i.e., cancer, cell aggregation-induced embolism or stroke, ectopic tissue formation, disease transmission), while not zero, is exceptionally low in practice and largely theoretical at this point;
- With the exception of maintaining sterility, the risks associated with short-term expansion (through ~p5) are relatively low and can be managed effectively through the use of closed loop systems or modest QA programs;
- While efficacy may vary with cell purity or dosing, there is little risk from a safety perspective in delivering a mixed population of autologous cell types across a wide range of dosages. Similarly, there does not appear to be a safety issue associated with cell-viability;
- The tolerance for risk in target patient populations is directly linked to the severity of the disease and the likelihood of recovery with standard medical therapy;
- While there is a precedent for regulating CBTs under the practice of medicine (i.e., *in vitro* fertilization [IVF]), there is no state medical board framework in place today to train or monitor physicians in the safe isolation and delivery of CBT;
- Few prospective patients are adequately informed of the potential risks and benefits associated with CBTs;
- While those in the field may assign various values to animal studies, many would agree that animal studies are not as predictive of human safety or efficacy as the FDA might suggest. Animal studies with CBTs do disappointingly little to alleviate risk or convey efficacy in human models, and there is no real substitute for slow, measured progression through initial human studies. While admittedly a controversial concept, it is more likely that the most efficacious protocols will be derived from careful, controlled and monitored human studies rather than a Geron-like progression through hundreds of rodent studies.

These points do not, however, in any way condone the unregulated free-for-all that has evolved in many parts of the world. Rather, we propose a new system that recognizes the strengths and weaknesses of classic drug clinical trials, values physician innovation and strives to balance patient risk with potential benefit. This new regulatory framework would mimic elements of the FDA's existing tiered structure (Class I, II and III), recognizing the risk–benefit differences between a marrow-derived injection for critical limb ischemia and intravenous injections for vague afflictions such as 'aging'. It should not, however, preclude largely investigational therapies for debilitating diseases, such as Parkinson's or Alzheimer's, even though there may be relatively little evidence for efficacy. Indeed this type of controlled clinical 'experimentation', though largely absent in the USA now, has driven some of the most prolific periods of medical innovation. It would, however, require appropriate quality control guidelines, and perhaps most importantly, establish reporting requirements for data collection. Whether under the umbrella of the FDA or State Medical Boards, we would establish a regulatory framework for autologous therapies that establishes:

- Basic quality assurance guidelines to target the most prominent risks associated with manipulating cells (training, tracking, sterility, cross-contamination). These guidelines would require GMPs akin to those used in IVF but would not encumber a physician to perform years of benchtop research to identify the optimal cell concentration, cell population ratios and mechanistic data;
- A tiered risk–benefit ratio for all therapies that would drive a consistent informed consent process. A patient would clearly understand the differences in efficacy for treatments for Alzheimer's or Parkinson's versus those for myocardial regeneration or critical limb ischemia;
- An independent accreditation process to give patients a tool to seek only physicians who have been adequately trained in the harvest, processing and delivery of cells and whose facilities and protocols have been properly evaluated;
- A mandatory data collection registry that captures patient outcome data and that would be shared with healthcare authorities to monitor different protocols for differential evidence of safety and efficacy.

Over the last 5 years, thanks in large part to an alarmist focus on largely hypothetical risks, autologous stem cell therapies delivered under the umbrella of the practice of medicine have been portrayed as 'snake oil'. While there is admittedly no shortage of examples where this image is true, it is clear that this broad brush should not be used to paint the entire field. Moreover, the real risks do not need to be managed by a regulatory framework designed for mass-produced, allogeneic therapies. Sadly, some of the US clinics that have developed ideal models for quality assurance systems and safety controls have been attacked and derided

for failing to live up to FDA investigational new drug application standards. These illogical and counterproductive attacks simply drive patients abroad where standards are nonexistent. Our objective should be to allow US-based stem cell clinics to deliver therapies with reasonable safeguards (that are not the same as drug manufacturers, and do not strive for zero risk) to adequately informed patients in a transparent fashion. Assuming that allogeneic and autologous treatments should be regulated the same is a disservice to patients everywhere.

Ultimately this debate has many parallels with the evolution of organ transplantation. Imagine today, the barriers a physician would face in developing successful transplantation protocols under the framework of the FDA. Indeed, physician innovation and significant clinical risks were certainly a major driver behind the success that the field enjoys today. Arguing against point-of-care therapeutics while holding up the sensationalistic banner of rogue clinics is a bit like trying to curb the transplantation field over concerns of organ trafficking. While one can debate *ad nauseam* over whether the FDA or state medical boards can best manage an improved regulatory framework, it would seem clear that the FDA's existing framework works poorly for these autologous applications. State medical boards, have, in contrast, proven quite effective at delivering other CBTs as exemplified by the IVF model [19]. Irrespective of which agency acts as the watchdog, it is clear that an improved system with a rational policy toward risk–benefit would be a dramatic benefit to patients. As we contemplate the structure of new regulatory frameworks, we must be mindful of the very clear financial conflicts of interest held by industry, the physicians and academia.

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