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From Bench to FDA to Bedside: US Regulatory Trends for New Stem Cell Therapies

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Abstract

The phrase “bench to bedside” is commonly used to describe the translation of basic discoveries such as those on stem cells to the clinic for therapeutic use in human patients. However, there is a key intermediate step in between the bench and the bedside involving governmental regulatory oversight such as by the Food and Drug Administration (FDA) in the United States (US). Thus, it might be more accurate in most cases to describe the stem cell biological drug development process in this way: from bench to FDA to bedside. The intermediate development and regulatory stage for stem cell-based biological drugs is a multifactorial, continually evolving part of the process of developing a biological drug such as a stem cell-based regenerative medicine product. In some situations, stem cell-related products may not be classified as biological drugs in which case the FDA plays a relatively minor role. However, this middle stage is generally a major element of the process and is often colloquially referred to in an ominous way as “The Valley of Death”. This moniker seems appropriate because it is at this point and in particular in the work that ensues after Phase 1 clinical trials that most drug product development is terminated, often due to lack of funding, diseases being refractory to treatment, or regulatory issues. Not surprisingly, workarounds to deal with or entirely avoid this difficult stage of the process are evolving both inside and outside the domains of official regulatory authorities. In some cases these efforts involve the FDA invoking new mechanisms of accelerating the bench to beside process, but in other cases these new pathways bypass the FDA in part or entirely. Together these rapidly changing stem cell product development and regulatory pathways raise many scientific, ethical, and medical questions. These emerging trends and their potential consequences are reviewed here.

Conflict of interest declaration

The author has no conflicts of interest.

Introduction

The objective of this review is to provide a concise discussion of the key issues involved in US regulatory oversight of stem cell-based biological drug development by the FDA with an emphasis on emerging trends that converge on the shared goal of accelerated translation to the clinic. This discussion will include consideration of the actual regulations and of emerging areas such as accelerated regulatory review mechanisms, compassionate use, and right to try laws. These latter evolving approaches seek to avoid therapy pipeline failure in the Valley of Death phase [1] and to promote relatively rapid advancement of therapies to patients in need. The growing and concerning trend of dubious stem cell clinics skipping regulatory oversight completely or almost entirely in the US and already selling “stem cell” interventions to patients will also be discussed in the context of the risks they pose both to patients and to the regulatory scheme overall as well as to the stem cell field more broadly. Specific examples of stem cell products going through the more conventional, compliant process in the US currently will be discussed as well including the products and regulatory experiences of Geron [2], BioTime [3], and Advanced Cell Technology (ACT), with discussions of other companies as they apply to specific regulatory mechanisms or product types.

FDA biologics regulations: to be a drug or not be a drug?

In the US, human biological products are generally classified in two broad categories: (1) human cellular and tissue products (HCT/Ps) that are minimally manipulated and used clinically in a homologous manner (termed “361s”) and (2) HCT/Ps that are either more than minimally manipulated or used in a non-homologous manner (termed “351s) or both [4]. The latter kind of product is defined as a biological drug and is subject to regulation by the FDA much the same as other more traditional chemical drug products. Biotech companies producing stem cell products typically produce 351 biological drugs that by law must go through the multi-phase drug pipeline approval process starting after pre- clinical studies with an Investigational New Drug (IND) application and proceeding to Phase 1 trials and so forth (Figure; black arrow). However, even some biotech companies and physicians at Universities are starting to show more interest in the clinical use of products that might fit into the 361 designation. It is important to emphasize that the 361 designation is appropriate for some stem cell-related products meaning a lesser role for the FDA in the vetting process and speedier translation to the bedside.

The term “more than minimal manipulation” is a critical element to the determination of whether a production is a 351 or 361. The question used to determine whether a product is minimally manipulated or more than minimally manipulated asks whether the inherent biological nature or structure of the material has been altered significantly. For example, enzymatic dissociation of a tissue such as adipose tissue or the addition of distinct chemical or biological elements to the product would generally trigger classification as “more than minimal manipulation”. There are some exemptions to this framework as, for example, treatment of a product with antibiotics, clearly a foreign substance, is not technically considered more than minimal manipulation. The same may be true for centrifugation of a product. The apparent rationale behind these exceptions is that these manipulations are

either unavoidable or have been demonstrated to not significant change the safety profile of the resulting product. Timing is another issue as the longer a product isolated from the human body is kept in a laboratory, for instance, prior to ultimate use in a patient, the more likely it is to be considered more than minimally manipulated, but there are indications that manipulations are of more importance to the FDA than timing.

The issue of non-homologous use is also central in the biological drug development process in the US. Even if products are not more than minimally manipulated, if they are used in a non-homologous manner, they are in general automatically considered 351 biological drugs requiring an IND. An example of non-homologous use would be a clinical intervention based on an adipose derivative product for patients with the nervous system disorders Multiple Sclerosis (MS) or Amyotrophic lateral sclerosis (ALS). In this instance, adipose tissue has no homology to the tissues of the nervous system, and the logic then is that non-homologous use of an adipose-derived product to treat an unrelated tissue poses higher inherent risks since the product is in a sense on one important level foreign to the target tissue.

Default Deregulation: Proliferation of non-compliant stem cell clinics as a serious challenge to FDA regulatory authority?

While non-homologous use is a very important element of regulatory oversight of stem cell-based biologics, for-profit stem cell clinics are challenging the non-homologous concept. The vast majority of stem cell biotech companies in the US have 351 products in development and do not dispute this classification of their products as biological drugs. However, an alarming number of smaller, direct-to-consumer for-profit stem cell clinics are already “treating” patients with products that in many cases potentially could be unapproved 351 biological drugs. These clinics generally self-classify their products as 361 HCT/Ps or claim that they are simply part of the “practice of medicine” not subject to FDA regulation. They then forgo the regulatory process entirely (Figure, red arrow) despite in many cases also using these products in a non-homologous manner. Such clinics pose a destabilizing threat to the overall regulatory framework in the US. In addition, these stem cell clinics may put patients at risk because they avoid regulatory oversight and their care providers generally lack adequate formal training in stem cells [5, 6]. Concerns have been raised as to whether the FDA lacks sufficient resources to appropriately regulate the growing American stem cell clinic industry given the relatively static FDA budget. An alternative explanation for FDA inaction recently is that it reflects a change in philosophy at the FDA to a less confrontational, more permissive approach to regulating the for-profit stem cell clinic domain, perhaps to avoid litigation.

Surprisingly, to date in 2014, in terms of documentation available in the public domain, the FDA has taken no formal regulatory actions against stem cell clinics in the US even as the number of clinics rapidly continues to grow, while in past years it had issued warning letters to a number of such clinics. Adding to this regulatory puzzle of reduced FDA action this year is the fact that in January 2014, the FDA won a critical federal court case (*US v. Regenerative Sciences Inc.*) that explicitly empowers the FDA to regulate laboratory-grown stem cell products as 351 biological drugs [4]. In principle such as a legal victory could have

been expected to lead to more, not less FDA action on stem cell clinics using potentially unapproved stem cell-based biological drugs. The growing number of potentially non-compliant stem cell clinics and their practical use of potentially unapproved stem cell-related biological drugs together pose a serious challenge to the FDA. The recent span of apparent relative FDA inaction on non-compliant stem cell clinics in effect could be leading to the creation of "default deregulation", an unfortunate scenario in which the operational practices of clinics in a relatively unregulated setting render official regulations inactive and subordinate to clinic practices. The relative lack of regulatory action recently on stem cell clinics leaves physicians and the broader community to largely distinguish between such clinics and approved devices on their own. In that regard, clinics utilizing unapproved devices and drug products may be identified by a lack of affiliation with academic medical institutions, relatively few if any publications, and generally no IND.

What more specifically is involved in the more traditional biological drug regulatory process that dubious stem cell clinics seek to avoid? There are a number of steps involved that require time, effort, and money toward the goal of advancing evidence-based medicine. In the compliant pipeline, once a product is defined as a 351 or 361 and as appropriate, an IND is submitted, the next major hurdle is obtaining approval to start a Phase 1 clinical trial. The FDA may require additional pre-clinical data before approving the start of a Phase 1 trial.

Advancing Adult Stem Cell Therapies

Encouragingly, a growing number of adult stem cell products are being studied in clinical trials for a wide variety of health issues including urological conditions. There are three hundred and twenty-eight trials listed for a Clinicaltrials.gov search of "Stem Cells AND Kidney"[i] as well as thirty-three for "Stem Cells AND Urological"[ii], and most of these trials are based on the use of adult stem cells. For example, Cook MyoSite has a number of adult stem cell clinical trials at various stages for incontinence[iii] and two recent publications report strong safety profiles and hints at efficacy [7, 8].

Adult stem cells have a number of potential advantages over pluripotent stem cells including a generally better, proven safety profile from a tumorigenesis perspective. There may also be lower risks with the use of adult stem cell-based therapies in terms of the potential negative outcome of non-tumorigenesis, but potentially still harmful growth of an undesired tissue type. Adult stem cell therapies also may more simply and commonly be used in an autologous manner, making immunosuppressive therapy unnecessary. For these reasons, from a general perspective the regulatory oversight process for adult stem cell biological therapies can be in some circumstances relatively more straightforward.

Geron: an open, then shut, and then open stem cell case

A number of biotechs are nonetheless advancing pluripotent stem cell-based products and these may address important disease states in unique ways. For example, the company Geron was producing and conducting preclinical rodent studies on the first human

[i] http://clinicaltrials.gov/ct2/results?term=stem+cells+AND+kidney&Search=Search
[ii] http://clinicaltrials.gov/ct2/results?term=stem+cells+AND+urological&Search=Search
[iii] http://clinicaltrials.gov/ct2/results?term=Cook+Myosite&Search=Search

embryonic stem cell (hESC)-based product, GRNOPC1, intended for use in treating patients with spinal cord injury (SCI), the FDA required additional data to address the issue of cyst development and placed a hold on GRNOPC1 process pending the new data. Ultimately this cyst issue was resolved as not posing a likely health risk and the first in-human hESC-based study began, but still this delay was significant. It likely put financial stress on Geron and slowed the overall process. At the same time, one could argue that the FDA action was important for ensuring the best chance of product safety without actual human subject data. While the FDA-approved Geron trial was in its infancy, the company decided to stop its SCI trial entirely, leaving open the question of whether the lengthy and expensive approval process for GRNOPC1 played a role in this decision [9]. After a period of limbo of a couple years, the BioTime subsidiary Asterias recently purchased the Geron stem cell portfolio including GRNOPC1 and is on track to resume the trial [3].

Other Pluripotent Trials

Following close behind Geron on the hESC trail in the US was Advanced Cell Technology (ACT), which shortly after Geron received FDA approval for combined Phase 1/2 clinical trials of its hESC drug retinal pigmented epithelial cell (RPE) product for treatment of macular degeneration (MD). The FDA experience with pluripotent stem cell product development and oversight with Geron was further deepened with ACT's progress through the pre-clinical and now early clinical phases. ACT currently still has two related combined Phase 1/2 clinical trials ongoing for treatment of MD using RPEs made from hESC. To date, no major stem cell-related adverse outcomes have been reported from either Geron or ACT patients who received hESC-based treatments [10, 11]. In the near future, both ACT and BioTime will likely face the Valley of Death phase of the stem cell product regulatory oversight process, leaving open the question of how they will navigate this often lethal stage. Following in the footsteps of ACT and BioTime is ViaCyte, which is setting its stem cell sights on Type I Diabetes. ViaCyte has developed an encapsulated hESC-based product for maintenance of blood sugar in Type I diabetics, for which an IND was recently approved by the FDA clearing the way for beginning a Phase 1 trial.

Evolving FDA mechanisms for stem cell therapy acceleration to the bedside in the US

The trend toward accelerating the study of still investigational stem cell products in human patients is also manifesting in the US in a number of ways. The FDA itself has a number of evolving mechanisms for speeding bench-to-bedside translation of drugs more broadly that may be utilized as potential routes to more expeditious translation of stem cell-based or any other therapy to patients. These mechanisms include Fast Track [12], Breakthrough Therapy Designation [13], Accelerated Approval [14], and Priority Review (Figure, orange arrow).

The FDA defines Fast Track as “a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need” with the purpose being to “get important new drugs to the patient earlier.” Fast Track would seem ideally suited for innovative new biological drugs based on stem cells and there are certainly serious conditions and unmet medical conditions potentially treatable by investigational stem cell products. A significant number of stem cell products are currently being evaluated via Fast Track[iv], but it is an experimental regulatory approach so a thorough understanding

of its effectiveness and potential impact on patient safety awaits further outcomes. Accelerated Approval is in some ways a similar program, but one specifically designed to get to the endpoint of approval and based upon a surrogate endpoint instead of a clinical endpoint. The example the FDA uses is of a drug that causes tumor shrinkage (the surrogate marker) but has not yet shown the clinical benefit of prolonging patient survival. The Accelerated Approval regulations could apply in such a case. Priority Review is another option for expediting regulatory oversight processes. In the context of Priority Review, the FDA is required to take action in only 6 months rather than 10 months via priority commitment of greater agency resources[v].

Breakthrough Therapy designation was created in 2012 by the FDA and is the newest acceleration-related mechanism. It is a unique functional way for the FDA to define an emerging therapy such that it receives expedited development and review, for example, via Fast Track. The Breakthrough Therapy designation requires that there already be existing preliminary initial data on the drug suggesting it is a “substantial improvement” over the therapeutic status quo. No investigational stem cell therapies have, as of September 2014, ever received Breakthrough Therapy designation.

Compassionate Use

One of the hottest and most controversial topics globally in the area of accelerating stem cell therapies to patients is compassionate use (Figure, green looping arrow that bypasses Phases 2 and 3 of the clinical trials approval process). In the US, the FDA does consider requests for compassionate use (what it terms “expanded access”) for investigational biological drugs such as stem cell-based therapies on a case-by-case basis for patients with terminal illnesses. In this scenario, the patient's physician and the drug manufacturer must both agree to the proposed compassionate use and gain authorization from the FDA. Drug manufacturers may be reluctant to approve compassionate use as it can potentially complicate the approval process for their drug. Even so there are currently 122 open studies that allow for “expanded access” compassionate use of investigational drugs[vi]. Nine are stem cell-related studies of which seven trials have an “Available” status[vii]. Of these most are in the US (recall that the clinicaltrials.gov website includes trials from all around the world) and are related to hematopoietic stem cell transplants, but interestingly one is for cartilage tissue engineering.

The experience with compassionate use of stem cell interventions in Italy involving the Stamina Foundation may also end up having major impact more globally including in the US. The drug regulatory framework in Italy is distinct and allows for more compassionate use of investigational products. The Stamina Foundation in Italy began experimental stem cell treatments on many patients including children under the rubric of compassionate use. This led to the explosion of a political and social controversy that continues to this day even

[iv] http://www.cirm.ca.gov/sites/default/files/files/agenda/Fifteen_Cell_Therapies_PhaseIII_Clinical_Trials.pdf
[v] http://www.fda.gov/forpatients/approvals/fast/ucm405405.htm
[vi] http://www.clinicaltrials.gov/ct2/results?term=%22Expanded%20Access%22%20[STUDY-TYPES]&recr=Open
[vii] http://www.clinicaltrials.gov/ct2/results?term=%22Expanded+Access%22+%5BSTUDYTYPES%5D&recr=Open&rslt=&type=&cond=&intr=stem+cell&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&gndr=&rcv_s=&rcv_e=&lup_s=&lup_e=

though the Italian health ministry's national institute (ISS) and the Italian Medicines Agency (AIFA) recently prohibited Stamina treatments because of safety concerns [15-17]. In large part the Italian authorities stepped in to take action to protect patients in the Stamina case because of the unusual public stances taken by Italian scientists including in particular Paolo Bianco, MD, Elena Cattaneo, PhD, Michele De Luca, MD, and Luca Pani, MD. Cattaneo, Bianco and De Luca together received the 2014 ISSCR Public Service Award [16] for their actions in the Stamina case. It seems likely that the Stamina case may make the FDA more reluctant to allow broader application of compassionate use in the US. However, the FDA has not commented on the Stamina case, and reportedly, the FDA grants greater than 99 percent of expanded access requests [18].

Right To Try Laws

Another notable development in the arena of accelerating investigational therapies to patients in the US has been the emergence of so-called “Right To Try” (RTT) laws [18]. While several state legislatures have passed RTT laws, it remains unclear how these laws could actually function given that they appear to conflict with regulatory rulings by the FDA, which is empowered by federal law. Typically in the US, federal laws of the kind that give the FDA the authority to regulate and approve (or not) specific investigational new drugs such as emerging stem cell products would have preempt state laws such as the RTT laws[viii]. Essentially, RTT is a state regulatory experiment that is predicted to lead to conflict in the courts due to its apparent incongruity with federal law and indeed arguably one intentional purpose of RTT is to provoke a legal challenge to the authority of the FDA. Nonetheless, several states appear poised to move forward with patient treatments based on RTTs. For example, in Colorado, which has a RTT law currently in place, a patient could in theory receive an investigational stem cell treatment that has not been approved by the FDA.

The main requirements for RTT to be invoked are that the patient must be gravely ill and the stem cell drug product in question must have successfully demonstrated a minimum level of apparent safety in an FDA-approved Phase 1 clinical trial, but does not require Phase 2 or Phase 3 data (Figure, green looping arrow). One specific company, Neuralstem, has indicated some potential interest in treating ALS patients via RTT in Colorado. Neuralstem currently has a stem cell product in a Phase 2 trial for ALS. Neuralstem has indicated that it will not go ahead with RTT for ALS patients in Colorado if told by the FDA not to proceed. However, it remains unclear if Neuralstem would proceed if the FDA had not officially said “no”, but also at the same time had not said “yes” (i.e. explicitly given permission) for the company to proceed. It is crucial to factor into this equation the fact that the life expectancy of ALS patients is usually only a few years from diagnosis and there are no currently available effective treatments for ALS. Thus, ready access to experimental therapies that arguably could be made possible by RTT in Colorado is important to the ALS patient advocacy community.

[viii] http://books.google.com/books?id=Si0lupMPrEoC&pg=PA31&dq=federal+preemption&lr=&as_drrb_is=q&as_minm_is=0&as_miny_is=&as_maxm_is=0&as_maxy_is=&as_brr=3&ei=8LIxStCZBZLqyASuyJW6Bg#v=onepage&q=federal%20preemption&f=false

Stem Cell Tourism

ALS patients in states without RTT laws have indicated some level of interest in traveling to Colorado for treatment, but some patients from North America are willing to travel much farther including outside the US to seek stem cell interventions for their health conditions [19]. In some cases, this “stem cell tourism” has led to the deaths of patients even as they are trying to improve their health abroad [20]. Stem cell tourism is often promoted via patient testimonials on the Internet and via social media [21]. There is no evidence that the products or procedures sold by stem cell tourism clinics are safe or effective. Even so it seems likely that stem cell tourism will be continue to be exploited by dubious stem cell providers as a mechanism to avoid FDA oversight. Stem cell researchers, societies, and governmental officials both inside the US and around the world seem largely stumped as to how to address stem cell tourism and the broader trend of medical tourism.

Summary

Efficiently translating emerging new stem cell therapies to patients, particularly gravely ill patients, is a high priority in the US and elsewhere in the world. Regulatory agencies such as the FDA are increasingly invoking new regulatory mechanisms for accelerated review of investigational new drugs and it is likely that these mechanisms will be applied specifically to new stem cell biological drugs. At the same time, other mechanisms outside of the FDA including the burgeoning dubious stem cell clinic industry in the US, state RTT laws, and other approaches such as stem cell tourism seek to speed up the process further based on various agendas, some more meritorious than others. Taken together, these factors and events lead to intriguing situations both in the US and elsewhere in the world. At present, multiple regulatory experiments related to emerging stem cell therapies are underway that will not only inform, but also in part conflict with each other. It will be critically important to follow how this regulatory experimentation play out in parallel to how the actual stem cell biomedical and clinical experiments themselves proceed as well.

References

1. Dorey E. Awards bridge ‘valley of death’. Nature biotechnology. 2009; 27:678.
2. Strauss S. Geron trial resumes, but standards for stem cell trials remain elusive. Nature biotechnology. 2010; 28:989–990.
3. Brower V. BioTime acquires Geron's stem cell program. Nature biotechnology. 2013; 31:94.
4. Sipp D, Turner L. Stem cells. U.S. regulation of stem cells as medical products. Science. 2012; 338:1296–1297. [PubMed: 23224541]
5. Knoepfler PS. Key action items for the stem cell field: looking ahead to 2014. Stem cells and development. 2013; 22(Suppl 1):10–12. [PubMed: 24147571]
6. Knoepfler PS. Call for fellowship programs in stem cell-based regenerative and cellular medicine: new stem cell training is essential for physicians. Regenerative medicine. 2013; 8:223–225. [PubMed: 23477401]
7. Peters KM, Dmochowski RR, Carr LK, Robert M, Kaufman MR, Sirls LT, Herschorn S, Birch C, Kultgen PL, Chancellor MB. Autologous muscle derived cells for treatment of stress urinary incontinence in women. The Journal of urology. 2014; 192:469–476. [PubMed: 24582537]
8. Carr LK, Robert M, Kultgen PL, Herschorn S, Birch C, Murphy M, Chancellor MB. Autologous muscle derived cell therapy for stress urinary incontinence: a prospective, dose ranging study. The Journal of urology. 2013; 189:595–601. [PubMed: 23260547]

9. Brindley D, Mason C. Human embryonic stem cell therapy in the post-Geron era. Regenerative medicine. 2012; 7:17–18. [PubMed: 22168491]
10. Schwartz SD, Hubschman JP, Heilwell G, Franco-Cardenas V, Pan CK, Ostrick RM, Mickunas E, Gay R, Klimanskaya I, Lanza R. Embryonic stem cell trials for macular degeneration: a preliminary report. Lancet. 2012; 379:713–720. [PubMed: 22281388]
11. Schwartz S, Regillo C, Lam B, Eliott D, Rosenfeld P, Gregori N, Hubschman J, Davis J, Heilwell G, Spirn M, Maguire J, Gay R, Bateman J, Ostrick R, Morris D, Vincent M, Anglade E, Del Priore L, Lanza R. Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. Lancet. 2014
12. Vastag B. Tuft's report backs FDA fast-track, but post-marketing concerns loom. Nature biotechnology. 2006; 24:478.
13. Sherman RE, Li J, Shapley S, Robb M, Woodcock J. Expediting drug development--the FDA's new “breakthrough therapy” designation. The New England journal of medicine. 2013; 369:1877–1880. [PubMed: 24224621]
14. Cloughesy T. FDA accelerated approval benefits glioblastoma. The Lancet. Oncology. 2010; 11:1120. [PubMed: 21126686]
15. Garattini S, Remuzzi G, Vago G, Zangrillo A. Stamina therapies: Time to call a halt. Nature. 2014; 506:434. [PubMed: 24572416]
16. Bianco P, Cattaneo E, De Luca M, Pani L. Stamina therapies: Let the record stand. Nature. 2014; 506:434. [PubMed: 24572414]
17. Negrini S. Research and scientists, the media and the disabled, politicians and judges, actual real treatments and possible false hopes: a PRM perspective on the Italian Stamina Foundation case. European journal of physical and rehabilitation medicine. 2013; 49:761–763. [PubMed: 24522000]
18. Servick K. Patient advocacy. ‘Right to Try’ laws bypass FDA for last-ditch treatments. Science. 2014; 344:1329. [PubMed: 24948714]
19. Master Z, Robertson K, Frederick D, Rachul C, Caulfield T. Stem cell tourism and public education: the missing elements. Cell Stem Cell. 2014; 15:267–270. [PubMed: 25192461]
20. Turner L. News media reports of patient deaths following ‘medical tourism’ for cosmetic surgery and bariatric surgery. Developing world bioethics. 2012; 12:21–34. [PubMed: 22420449]
21. Levine AD. Insights from patients' blogs and the need for systematic data on stem cell tourism. The American journal of bioethics : AJOB. 2010; 10:28–29. [PubMed: 20461641]

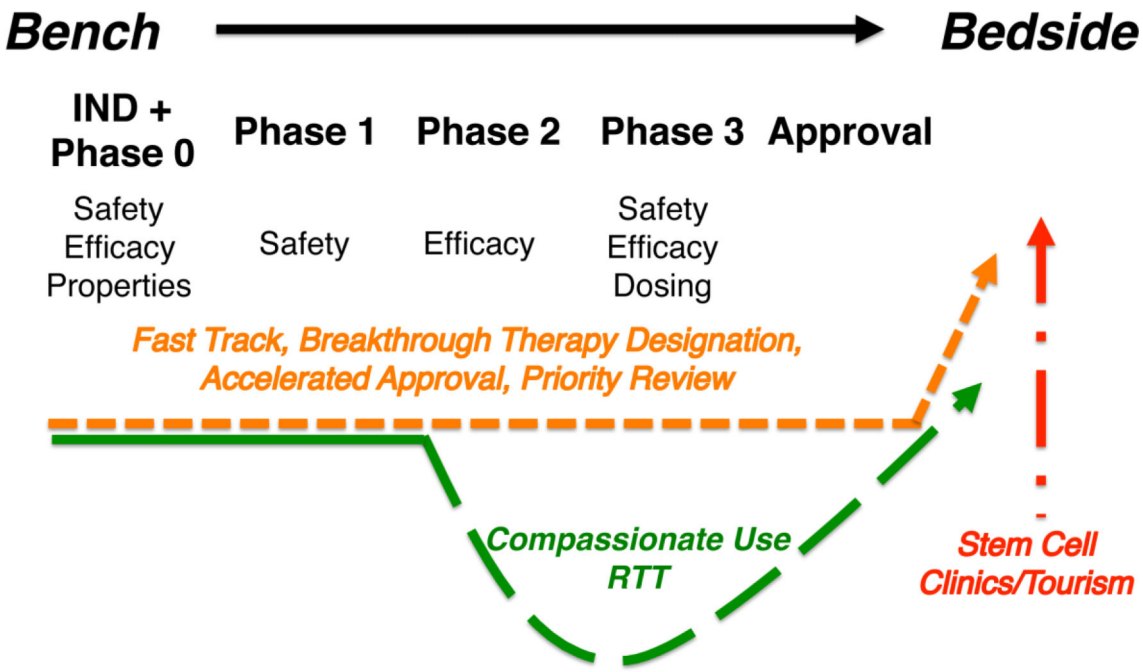

Figure 1.

Diagram of the evolving clinical trials process and other mechanisms of therapy translation to the bedside. The traditional, multi-phasic FDA clinical trials process is shown in black with a black arrow from bench to bedside. Evolving FDA mechanisms for accelerating the clinical trial process are shown in orange. Compassionate Use (also known as “Expanded Access”) and Right To Try (RTT) are shown in green with a loop reflecting the bypassing of Phase 2 and Phase 3. It is notable that the requirements for Compasionate Use are evolving and there are diverse stakeholder views. The precise pre-requisites (e.g. Phase 1 versus Phase 2 data) obtainable from FDA guidance are not completely clear and may vary on a case-by-case basis. The common stem cell clinic approach of entirely avoiding the clinical trials approval process is shown in red. Note that for some non-more than minimally manipulated stem cell products used in a homologous manner, direct use by stem cell clinics or other physicians may be appropriate with only a relatively minor role for the FDA.