stem cell translation and bioethics

During the last three decades, considerable hope and attention has led to the initiation of the field of "regenerative medicine". This has resulted not from the development of our ability to regenerate any organ or tissue, with the exception of the hematopoietic system-as widely believed, but only from the prediction that certain cells referred to as stem cells show the capacity *in vitro* to apparently undergo differentiation into cells of all the three germ lineages when cultured under various conditions. Such stem cells have been found in embryos, in fetal tissue and cord blood, in the placenta, in post-natal bone marrow, fatty tissue, blood, and practically everywhere else. The ethical restrictions on the use of embryonic stem (ES) cells are, in our opinion, ill-advised and inconsistent with nature. While well founded, this limitation has resulted in diminished progress in evaluation of ES cells for regeneration and it has spawned a new endeavour to generate embryonic-like stem cells from non-embryonic tissue. Be that as it may, the common thought that were not for regulatory issues, stem cell therapy would now provide a viable approach to many (if not most) diseases is often argued as a flawed concept. In fact, no reliable evidence exists that stem cells i.e. embryonic, induced or adult, have ever regenerated any tissue *in vivo*. In parallel, evidence for post natal trans-differentiation in humans is remarkably thin. One could easily make a case that this response does not occur and that the apparent trans-differentiation of mesodermal stem cells to cells of the ectoderm and endoderm are laboratory artefacts. On the other hand the field has seen remarkable progress in understanding of cell proliferation and differentiation.

Contrary to popular opinion, neither adult nor embryonic stem have to date shown significant potential for regeneration of any tissue other than the hematopoietic system. Complicating this fact are reports of transdifferentiation and reports of successful stem cell regenerative therapy. However no such claim has to date been verified and stem cell therapy remains, after almost 3 decades of research, hype that inspires hope (and expense) of desperate individuals with chronic diseases.

We contend that this hype has to be ceased immediately. Reports of stem cell promise based on their ability to generate

structures *in vitro*, or of their potential use after induction on "gene reprogramming" or other changes have clearly exceeded the data interpreted. The failure of stem cells to regenerate any somatic organ, tissue or cell testifies to the fact that hype in the lucrative businesses that have evolved to sell therapy before it is known to be effective has spawned almost 30% of the reports in biological science today. What these reports fail to mention is the fact that stem cell therapy has not succeeded. Gene reprogramming hasn't either.

Introduction

It is time for a change. Therapeutic strategies employing "stem cells" are said to be based on the success of hematopoietic stem cells when used to reconstitute the hematopoietic system. However, stem cell procurement, culture and infusion differ remarkably from methods which are successful for processing stem cells for restoration of hematopoiesis. In contrast, methods accepted for use of somatic (non-hematopoietic) stem cells would clearly prevent a hematopoietic stem cell transplant from succeeding. It is not at all clear why this has developed and is universally accepted but this defines a basic flaw in the production and use of stem cells therapeutically. We herein define the nature of that flaw and specify experimental approaches which must be taken to determine if these barriers can be overcome in order to parley stem cell therapeutically sound entity in clinical medicine.

I. Hematopoietic Restoration

What works:

Donor Cells: Non-adherent cells derived from bone marrow and cord blood, exclusively.

Preparation: Donor cells must possess the antigen CD34 to reconstitute the hematopoietic system.¹ Cryopreserved donor cells retain engraftment ability for at least 17 years. No reproducible system has been developed to culture hematopoietic progenitors without loss of repopulating ability. No adherent (and by definition cultured) "stem cell" has ever reconstituted hematopoiesis in an animal or a human unless injected with chimeric non-cultured stem cells.

What doesn't: Adherent stem cells or cultured hematopoietic cells.

Hematopoietic stem cells rapidly lose their repopulating ability when cultured under any condition.² One series of reports published in 2003 implies that hematopoietic stem cell progeny can restore hematopoiesis if the donor cells are infected with Homeobox-4a prior to culture but these reports have not led to clinical advancement anticipated if these results are viable. Other reports merely accept as "asked and answered" the notion that homeobox infected HSCs produce repopulating progeny in culture but it is doubtful that this is the case.³ There is, however, no doubt that cultured hematopoietic cells can contribute to the repopulation of all hematopoietic cell lines in an ablated host but only if the donor cultured cells are first mixed with fresh hematopoietic cells of the recipient. Importantly, no report has confirmed restoration of hematopoiesis with only cells derived from cultured hematopoietic "progenitors". Reports of chimeric reconstitution are limited to animal systems and utilize adherent cultured cells. No adherent hematopoietic stem cell has been reported to be able to reconstitute the hematopoietic system of humans and clinicians will not utilize any culture method in clinical transplantation.

II. Regeneration of non-hematopoietic tissues

What works: To date, nothing.

Why: Unknown.

However, belying the facts asserted in Table 1, many have been led to believe that the clinical efficacy, summarized in a recent essay of the "Potential" uses of stem cells, have already been achieved (Figure 1). This figure appeared on October 28, 2011 that sought customers for hair restoration clinic. This clinic takes a variety of approaches to hair restoration, and has recently added stem cell therapy to their repertoire of approaches.

Why not? Hair loss, loss of motility in the arm of a professional baseball pitcher, arthritis, neural disorders etc; every disease known to man in essence is "potentially" treatable with stem cells. But there is no scientific evidence that stem cells restore hair loss to male pattern baldness of cancer therapy and there is no evidence

Fig. 1: Recent advertisement from a commercial clinic that employs stem cells for therapeutic goals.

Fig. 2: Five milestones of stem cell research did not occur in any chronological order but were oddly random, as if orchestrated.

that stem cells are at all useful for human musculoskeletal disorders. In contrast, stem cell therapy consistently exacerbates symptoms of osteoarthritis. We are happy that the pitcher's arm is better, but attributing this to stem cells is purely anecdotal. But stem cell clinics, regardless of FDA regulations are raking in a lot of money, based on the "potential uses of stem cells".

Figure 1 is used as a come-on to get paying customers for a stem cell hair replace-

ment clinic (which probably operates outside the bounds of FDA regulation, but indeed operates), please notice that the title is "Potential uses of Stem Cells" with original caption "As noted above, stem cells can be utilized to treat many conditions". Most exciting is the ability to utilize this technology to treat hair loss in men and women. The body image then defines several foci of pathology, listing diseases that encompass more than a small majority of the diseases the citizens of the world today are very concerned

about. The figure explains why specialists in stem cell research have not risen to the occasion and dismissed the myth the image clearly leads the lay audience to endorse, that stem cells can cure Diabetes, Spinal cord injuries, Missing teeth, Crohn's disease, Multiple site cancers, Deafness, Muscular Atrophy, Alzheimers disease, Parkinsons disease, Stroke etc. The reason the FDA by inaction allows this myth to survive and thereby perpetuate it is complex. One reason is that the workload of the FDA is enormous and stem cell clinics are sprouting very quickly. But we here note that the FDA had no problem in global enforcement of the Bush ban on embryonic stem cell research for 10 years. The FDA could easily enforce their regulations that render stem cell transplants illegal, everywhere but don't. The question is why they allow this to continue; patients have died and sustained chronic injuries from this process to date.

The field has been defined by events rather than by experimental results. The five events that determined the pace of stem cell research are outlined in Figure 2. Let us here examine carefully the implementation, ramifications and enforcement world wide of the Bush Proclamation outlawing ES cell research.

President Bush, after great fanfare put an immediate end to Embryonic Stem Cell research throughout the world shortly after he was elected. In its short wording, the Bush proclamation only outlawed establishment of new embryonic stem cell lines in labs funded by the US government. Sixty- four cell lines all over the world were selected as so called potential cell lines as of August 9, 2001 and research on these cell lines was allowed to proceed. At the outset, investigators at UCLA, Harvard and other prestigious institutions declared their intent to bypass the ban by constructing facilities with private funds. Immediately, after the proclamation of President Bush, both Canada and England announced publicly and vigorously their intention of proceeding to develop new embryonic stem cell lines. Biggest action after Bush proclamation was California proposal 71 passed in 2004 led to the creation of California Institute of Regenerative Medicine (CIRM) to focus the then burning issue of embryonic stem cell research. It became the most expensive project in the history of research initiatives as 3 billion dollars funding was proposed.⁴ We recall that when Bush made this decision, embry-

onic human stem cells had only recently been identified and their clinical potential seemed enormous, too enormous.

As far as NIH – funded researchers went, a few, if any, complained about the potential scientific consequences of the ban, except the first author of this paper in the only editorial published in a scientific peer reviewed journal that merely questioned some of the consequences of the Bush proclamation.

Interestingly, the Bush Proclamation was hailed as a “brilliant compromise” by NIH staffers and many funded investigators of stem cell research. “A Brilliant Compromise” those exact same words were widely employed by the American press

to describe the decision President Clinton reached on a very controversial issue during his successful term. Many of the mainstream leaders of the field were invited to Washington DC the day Bush would make his announcement. For the most part, before they left, these individuals were sternly against this ban, and dreadfully afraid it would end all advance in stem cell research. They returned with a different attitude.

(.....to be continued in next issue)

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