stem cell translation and bioethics

(.....Continued from Volume 19 issue 3)

But why did Britain and Canada so quickly reverse their determined decision to ignore the ban? One could argue that these countries benefit from US aid and this extends to all their citizens. South Korea and other countries endorsed the ban with vigor at the delight of the President. But what about India, Iran, Iraq, China, Japan and other countries capable of developing this technology? Not one country or person defied the Presidential proclamation which was only supposed to apply to US funded research.

The motives to proceed were justified and well founded, and the ramifications of a total ban changed history, how was this accomplished? No one seems to know. Why was this so enforced, it doesn't take a lot of imagination to answer that question. What would evolve, was total control of stem cell research and its profits by governmental agencies who would choose, who was in, and who was not. NIH lost its capacity to render fair decisions on grant funding as monies were diverted to results that the government wanted to see transpire whether they did or not. The result is the mess the field now faces.

Scenario has changed after "U" turn taken on 9 March, 2009 by president Barack Obama, who officially cancelled bush proclamation allowing federal funding on human embryonic stem cell research.⁹ Sensitivity of internal politics was reflected when a federal district Chief Judge Royce Lamberth ruled against the stand taken by Obama administration saying that this will violate the Dickey-Wicker Amendment which prohibits federal funding for research that leads to the destruction of human embryo. Though further higher appellate court temporarily lifted the order of Royce Lamberth, sensitivity of the issue remains unchanged.¹

Cloning and Publication

The Presidential proclamation not only prevented progress in stem cell research, it prevented any attempt anywhere in the world to confirm the stunning results announced by the Hopkins research team. Since they did, those results stood unchallenged for nearly 8 years as the team opened a successful company called Geron in Baltimore that filed for pat-

ent rights to this clinical entity. Investors poured millions into Geron as new Biotech with similar goals sprouted and existing ones changed goals, including ACT in Boston.²

ACT or Advanced Cell Technology was led by Dr Michael West successfully for years. It is widely believed that a top publishing group would ask Dr West to be the Editor in Chief of a new, on line only journal that group developed as President of this group in New York, a firm with close connections to ACT. The Journal was titled "E-Biomed", and was careful to take extremely appropriate action to ensure manuscript review and the integrity of submitting authors. The Journal also relied on an extremely prestigious ethics committee that Dr West put together to oversee the research at ACT. The management of this group made no secret of their belief that on line communication of science was the wave of future and that print would soon be obsolete. Over this issue, a senior professor argued with management for hours on end; investigators want a print record of their findings he argued. The response of management was that E-Biomed would set the trend of the future, without doubt. Thus in early 2000, E-Biomed began with great publicity and fanfare. It went on to publish advances in gene transfer and tissue regeneration without problem for almost 2 years.

Then one day in the year 2001, a shocking event took place. After publishing a paper that was first to announce that human embryonic cell cloning was possible, a paper authored by Dr West and carried out at ACT, the journal ceased its publication and records were destroyed. A scandal erupted for no apparent reason. The Bush proclamation was not yet in effect, and the paper was first seen as a major advance. Dr West carefully noted that he destroyed the nuclear engineered embryo after only 2 or 3 cell divisions, and there didn't seem to be any readily apparent breach of ethics.

But the stem cell "in crowd" was furious when the on-line report appeared and management did not rise to defend its author/editor who management strongly supported till that day. Instead they ceased publication of their prized initial on line journal that they said would set the pace for future communication in science. ACT

had been a successful biotech that provided efficient and successful media for isolation of human hematopoietic stem cells which were used clinically and widely at that time. Dr Welmut had only recently cloned Dolly. No Presidential ban was in effect and President Clinton had no ethical problem with continued ES cell research. But someone was clearly upset.

Thus the ethics committee of ACT, which consisted of several prominent individuals, was furious. The chair of that committee, Professor Gearhart from Penn abruptly resigned his post in public indignation announcing only that the communication was dissemination of research results "by press release". Something clearly was amiss.

Dolly

The successful nuclear cloning of a human embryonic stem cell led to the prediction that like sheep, allegedly cloned in England by Dr Ian Welmut, humans were also amenable to cloning. In fact, this demonstration could lead to lucrative patents that would fail if the result was previously demonstrated. At the time, heated debates of the ethics of human cloning began. However, nuclear engineering or reprogramming held a lot of economic potential despite the fact that almost everyone agreed that no human should ever be cloned; a whole lot. And a lot of information was kept from the public.³

President Clinton remained silent but did not push ES cell research in his last 2 years in office. Most Senators announced that regarding this subject, they were "on the fence". A new President is elected and shortly thereafter manages to stop all ESC research in the world. The single critique of his ban was "profiled" and eventually silenced as Editor in Chief of the Journal he founded for the management as well as from his post as tenured Professor of Neurosurgery. The NIH refused to support his illegal termination and let him fend for himself against retaliation by USF and his former institution, Methodist hospital of Indiana in a well orchestrated plan that involved both the Prominent publishing house and NIH, as well as prominent investigators.

The Dolly Factor

One minor aspect that no one talks about is the fact that the foundation of everything we have come to accept about

stem cells rests really with Dr Welmut's successful cloning of a single animal, "Dolly". However what is not widely known is if Welmut successfully cloned anything. Based on accusations of staff, the investigation was itself investigated and inconsistencies were found. Since that research was privately funded, these were not widely reported. In the final analysis, Dr Welmut would admit "serious flaws" may have altered the results of the Dolly investigation in a manner that "would not be insignificant to the major conclusion of the paper". Meaning the results that were flawed in interpretation did significantly impact the major conclusion of the paper, that conclusion being the cloning of a mammal. Dr Welmut would not clone another animal. He instead rather curiously abandoned his work with embryonic stem cells announcing that the method he developed was too cumbersome, this after a single study. He would then join a group of selected scientists to try to create embryonic like stem cells from non-embryonic tissue, work that continues to this day for no apparent reason as human ES cells are now readily available.

Where do we go from here?

This commentary is not questioning the enormous future potential of embryonic stem cells but it is to point out business of selling hope by overhyping, where policy makers directly or indirectly, are equally responsible. Enormous potential of innocent stem cells are being exploited by clever & opportunistic group of beneficiaries as a tool to increase the liquidity of their bank accounts by selling hope of desperate patients in general and diverting the government as well as

private fundings in particular, which results in deviation from the ongoing novel research path.

In no way potential of stem cells can be questioned but hype should cease by taking scientific community and policy makers in the loop where former should have a greater say in this ever burning issue of stem cell translation.

Adult somatic cells can be reprogrammed to perform the functions similar to embryonic stem cells. Induced pluripotent stem cells (iPSCs) are considered to be potential therapeutic cells in regenerative medicine.⁴ Moreover human embryonic stem cells have its own limitations like ethical considerations and formation of tumours or teratomas from undifferentiated cells.⁵ iPSCs have morphological and functional similarity with hESCs with limited ethical concerns. Somatic cells can be used as a source to induce pluripotency. Pluripotency can be induced in differentiated cells by introducing some reprogramming factors like Oct3/4, Sox2, c-Myc, and Klf4, Nanog, LIN28.⁶ iPSCs can be differentiated to form patient specific cell type without using embryonic tissues.⁷ Transdifferentiation research is in progress in many places including developing countries like India though validation and comparison of iPSCs with hESCs in functional aspects is still to be achieved.⁸

Translation of this hype into dream stem cell centers for simultaneous research and clinical trials will be the key to achieve the future rational of curing fatal disorders following inflow of first tier brains into this field.¹⁸ Policy makers should think twice before taking any decision which can back-lash quality of life in general and humanity

in particular. iPSCs are the future beacon of light and hope in cell replacement therapies and regenerative medicine surpassing impediments of ethics and meeting the expectations of patients which is influenced by hype created by monetary beneficiaries of stem cell therapy.

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