2012 Guidelines for stem cell research

Express Pharma October (1-15), 41-44, 2012

Details
Category: Research
Saturday, 06 October 2012 18:43

***Dr BM Gandhi**, Chief Executive Officer, Neo BioMed Services, Former Advisor, Department of Biotechnology, Government of India, gives an insight about the draft guidelines for stem cell research released this March*


Dr B M Gandhi

The Draft Guidelines for Stem Cell Research 2012 were issued jointly by the Indian Council of Medical Research and the Department of Biotechnology in March 2012. They were developed against the backdrop of the perception that various clinics in India are offering largely unproven therapy, raising several ethical, legal and social issues and putting desperate patients at health and financial risks and that various studies in the West have shown that adult stem cells can cause severe complications. Apprehensions are raised that embryonic stem cells may cause further side effects in the form of cancer or tumours. It is further apprehended that in India, none of the treatment modalities have gone through rigorous clinical trials; there are no pre-clinical data on animal models available to ensure the safety of the treatments.

Apprehensions are raised that embryonic stem cells may cause further side effects in the form of cancer or tumour. It is further apprehended that in India, none of the treatment modalities have gone through rigorous clinical trials; there are no pre-clinical data on animal models available to ensure the safety of the treatments.

The significant difference the new Draft Guidelines presents is that there should be more emphasis on research and proof on concept before the stem cells are put to therapeutic applications. The Guidelines for Stem Cell Research and Therapy 2007 is now Stem Cell Research 2012. Guidelines prescribe strict procedures for sourcing and the use of stem cells by research institutions and provide ethical direction to scientists working in the field.

There is no any significant change in the areas being left out of research and applications except that more emphasis is given to basic research involving preclinical, clinical trials and clinical research to prove efficacy, safety and utility of the cell types used.

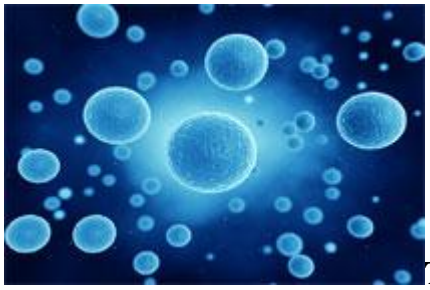
The Guidelines make it mandatory to run clinical trials for any use of stem cells for therapeutic applications even for types of cells prepared using standard established technologies and reagents. Stem cells using standard technologies have been commercialised worldwide and are being used for therapeutic use for a variety of disease conditions. The implementation of the new Guidelines may pose an imminent threat to commercial use as only very few of them have facilities for research and clinical trials. It would also give a set back to the established industry to

re-establish to meet the stringent requirement under the Guidelines to generate pre-clinical information and clinical trial data before commercialisation.

Given the present understanding, the strict compliance of the Guidelines would hold back thecommercial application of stem cells in India by another 7-10 years. It would also deny the beneficiaries the genuine treatment using the cell types prepared by standardised technologies. Most of the research in India is through public funding and restricted to major institutions doing basic research. They do not have much experience or capabilities of running clinical trials for which they are largely dependent on CROs/industry. Majority of members of the committees deciding on the fate of research and application of stem cell research in India are academicians with limited or no participation of industry.

Finalisation of the Guidelines 2012 thus would require further debate with the industry. A committee set up by the government agency should also study the side effects in form of cancer or tumour and reasons thereto by use of embryonic stem cells and other type of cells and do the risk benefit analysis. Regenerative medicine industry should also collectively come on a common platform in the form of a consortium to put forth constructive suggestions to improve the Guidelines.

Legal measures



The Draft Guidelines are still silent on how the absence of legal measures will be able to curb unethical stem cell medical practices. There is nothing in the Guidelines to outlaw, prohibit or punish those carrying out stem cell treatments. After the Guidelines are finalised, India will have a Bill to regulate stem cell practices. The Medical Council of India is supposed to regulate clinicians involved in unethical acts.

The Ministry of Health has prepared draft rules for umbilical cord blood banking under the Drugs and Cosmetics Act, 1940 and has put them up for pubic consultation. The new rules will govern cord blood stem cells.

Difference between the 2007 Guidelines and 2012 draft Guidelines:

The proposed Guidelines issued by the Department of Health Research and the Department of Biotechnology 2012 is still a draft.

Significant change from the previous Guidelines in 2007 (Guidelines for Stem Cell Research and Therapy) is that more emphasis is given to the research than therapy and hence the 2012 Guidelines are titled as 'Guidelines for Stem Cell Research.'

Reasons cited for the above are issues related to the use of human embryos to create human embryonic stem (hES) cell lines, danger of exploitation of underprivileged

people, and challenges related to prevention of human germ-line engineering and reproductive cloning, potential dangers of tumorigenicity in view of their potential for unlimited proliferation, possible genomic changes and immunological tissue incompatibility between individuals. To ensure safety and rights of those donating embryonic stem cells, additional basic and clinical research is suggested on foetal or adult stem cells to protect research participants from receiving unproven stem cell transplants.

The scope of the Guidelines has been extended to all stakeholders involved with basic and clinical research on all types of stem cells from humans whether autologous or allogenic, embryonic or foetal or adult, with or without manipulation. General principles would follow biomedical research involving human participants. Specific guidelines unique for stem cells have been suggested in view of their potential for unlimited proliferation, differentiation to tissues and cells of germ layers and their involvement in pre-implantation stages of human development in terms of procurement, regulated differentiation and pre-clinical and clinical research.

The research on human subjects, including human embryos and foetuses should ensure safeguarding of human dignity, human rights and fundamental freedom and practices related to obtaining human tissues and cells for research, diagnosis and therapy, fundamental tenets of beneficence, non-malfeasance, justice and autonomy would be guided by the general principles laid down in the Ethical Guidelines for Biomedical Research on Human Subjects by the ICMR.

Stem cells being unique, several specific scientific and ethical issues are to be addressed by the stakeholders by evolving specific principles to regulate stem cell research. Appropriate information needs to be provided to the potential donors while taking their consent of the invasiveness of the procedures, potential transmittable infections/diseases, possibilities of development of cell lines from their stem cells, banking and shared with others. They may also undergo genetic manipulation, and have potential for development of commercial products and that the intellectual property rights will not be of the donor.

The stem cells few in number require processing in terms of enrichment or in vitro expansion etc to obtain them in sufficient numbers. For embryonic stem cells or induced pluripotent stem (iPS) cells targeted differentiation may be required to generate the appropriate cells of interest. Being a biological product special considerations are required while choosing appropriate reagents/ media for developing quality assurance, safety while maintaining their potency and efficacy.

Special considerations are also required in terms of safety of the therapeutic products in view of the basic characteristics of stem cells of their potential for unlimited proliferation and ability to differentiate into a variety of cells and their ability to produce teratoma.

The Guidelines expands to add responsibilities of conduct of stem cell research to the sponsors of research besides investigators and institutions. Sponsors shall need to take note of their responsibilities and liabilities under various statutes and regulations governing research and development in the area in-force in the country. Sponsors would need to give maximum importance to review of research in this field to ensure highest degree of scientific rigor and resolution of ethical concerns. The

institutions would also need to ensure that the most current standards are applied for stem cell research and establish suitable mechanisms for creating awareness and communicating scientific evidences to the public. Institutional Committee for Stem Cell Research (IC-SCR) would have major responsibility to provide adequate support in view of limited expertise in the field. The physician/ scientist engaged in stem cell research shall ensure that no hype or unrealistic expectations is created in the minds of subjects or public at large regarding stem cell therapy. The basic scientists engaged in stem cell research from human sources shall safeguard human rights and human dignity to the donors.

The role of IC-SCR is expanded. Approval of IC-SCR would be necessary for creation of all new human pluripotent stem cell lines, irrespective of the source and methodology used; in-vitro studies on established pluripotent stem cell lines; in-vivo studies in experimental animals (other than primates) with established cell lines from any type of pluripotent stem cells; in-vivo studies on experimental animals (other than primates) using foetal/ adult somatic stem cells; establishment of new hES cell lines from embryos left unutilised in IVF programme and deposited in a cell bank for use by others; establishment of umbilical cord stem cell bank following guidelines for collection, processing, and storage etc.; clinical trials with clinical grade cells processed as per National GLP/ GTP / GMP guidelines.

Prohibited areas of research also include any in-vitro culture of intact human embryo, or any organised cellular structures that have the potential of developing into human organs and tissues, regardless of the method of its derivation, beyond 14 days or formation of primitive streak, whichever is earlier..

Basic research

Since stem cells derived from various sources are extensively being used in basic research for the fundamental understanding of their multiplication, differentiation to other cell types, drug discovery and screening research and clinical research/ trials for human disease, a new chapter on basic research has been added to the Guidelines. Depending on the source of their derivation and their differentiation capabilities, stem cells are classified into adult stem cells (ASCs) and pluripotent stem cells (PSC). On the basis of their origin, these cells have been classified in to different groups.

For basic research, a new class of human stem cells, human iPS cells, has been added to the list which are derived from foetal or adult diploid somatic cells by forced expression of pluripotency inducing factors such as Sox2, c-Myc, Oct-4 and Klf-2. They are genetically reprogrammed PSCs and they exhibit properties similar to a typical ES-cell line. Guidelines are also provided on experiments requiring IEC/ IC-SCR/ IAEC clearances.

Details on derivation and characterisation and potential applications of human pluripotent stem cells for basic and clinical research are also listed.

Other areas for basic research identified include modelling of human disease, drug development and derivation of a new hES cell line whether from spare embryos or embryos created for the purpose and necessary clearances required for the same.

A new chapter on preclinical and clinical trials and clinical research using stem cells has been added to the Guidelines. Guidelines are outlined for preclinical studies and clinical trials using stem cells for appropriate clinical applications involving the principles of clinical translation including ethical, social, clinical, scientific, and regulatory concerns and established standards of care for treatment. Details are provided preclinical study designs, approvals and monitoring, animal models, GCP/GLP; clinical research as laid down in the Schedule Y of Drugs and Cosmetic Act, GCP Guidelines of CDSCO and ICMR Ethical Guidelines, trial subjects, approval and monitoring, regulatory approvals, monitoring of clinical trials, potential use of stem cells for therapeutic purposes.

The guidelines have introduced a new chapter for the first time on tissue engineering and scaffolds in stem cell research. This chapter describes the recommended specifications and characterisation of raw or starting materials of natural and synthetic origin or their combination and a set of properties, which a scaffold must satisfy during the tissue regeneration process. The properties of biocompatibility of the material biodegradation into non toxic products, malleability to complicated shapes with or without appropriate porosity, ability to support cell growth and proliferation, and appropriate mechanical properties are also described. The raw materials and finished products should also meet the requirements of physicochemical properties, such as chemical identity, structure, topography, mechanical properties, thermal characteristics, sterilisability and biodegradation.

The Guidelines outlined in detail the criteria for biological evaluation of tissue engineering scaffold; physicochemical evaluation as per the procedures of American Society for Testing and Materials; and biological evaluation in terms of chemical characteristics of materials and the nature, degree, frequency and duration of its exposure to the body. Scope of the Guidelines covers primarily the materials and scaffolds that are used or new ones being developed for the delivery and in vivo functions of stem cells. Representative examples of scaffolding materials and synthetic tissues and biological substitutes include synthetic materials including biodegradable and degradable polymers; natural materials such as chitosan, alginate, collagen, albumin, hyaluronic acid, fibrin, de-cellularised tissues and peptides; biological substitutes from the extracellular matrix of human or animal tissues.

Another chapter has been included on defining the scope of banking standards of biological tissues, which included several models for banking of various biological tissues. Tissues of current interest in stem cell isolation and expansion are adipose tissues, Wharton's jelly, dental pulp, endometrial tissues, placental tissues etc. The Guidelines define standards for banking of umbilical cord blood and other tissues. Researchers are advised to adhere to suggested guidelines in the document and international standards, and regulatory documents for more information .

Additional information is provided for banking and distribution of cell lines. Cell lines from various tissues being used by researchers include embryonic stem cells (both normal and parthenotic), neonatal tissues (Wharton's Jelly), iPS cell lines, adult stem cell lines derived from mesenchymal stem cells, fibroblasts, myoblasts etc. The guidelines specifically outlined banking and distribution of hESCs.

New issues covered under the Guidelines are import / export of stem cells and public participation.

The Guidelines referred extensively to the international practices, procedures and technologies for basic research and applications of stem cells and ISO standards for biocompatibility testing of materials used in medical devices.

Conclusion:

1. Industry-sponsored stem cell research and therapy may not be subject to ICMR and DBT, when it is not funded by these organisations.
2. Separate body under DGCI, with academics and industry should be constituted, which will decide what should be done or not, keeping in mind the interest of public on the whole.
3. There are contradictions between perceptions of academia and industry . Since no patents are possible as a result, industry will not be able to get investors to fund stem cell research.

The author can be contacted at dr.bmgandhi@yahoo.co.in and drbmgandhi@rediffmail.com