EDUCATION, SCIENCE AND TRAINING

SENATE LEGISLATION COMMITTEE - QUESTIONS ON NOTICE
2003-2004 SUPPLEMENTARY BUDGET ESTIMATES HEARING

Outcome: 1
Output Group: 1

DEST Question No. E482_04

Senator Harradine asked on 5 November 2003, EWRE Hansard page 48:

Question:

Senator HARRADINE – I am asking you about proof of concept. What is the proof of concept? Could you provide us with what you were saying and, as it might save time, with what you said to the committee before it made its decision. It had before it a number of experimental studies on embryonic stem cells.

Prof Sara – We have previously provided you with all the published studies relating to both embryonic and adult stem cells.

Senator HARRADINE – I do not recall you providing me with anything in respect of human embryonic stem cells which showed that they were successful in treating disorders.

Prof Sara – As I said earlier, it is at an experimental stage. There is sufficient experimental data using both cell cultures and animal models to suggest that this is a worthwhile pathway for experimentation leading to a possibility for the treatment of very severe disorders.

Senator HARRADINE – I have asked you to supply that information.

Prof Sara – We can resupply it.

Senator HARRADINE – If you consider that it has already been supplied, then resupply it, please.

Prof Sara – Yes.

Answer:

Literature on treatment utilizing human embryonic stem cells

The ARC has provided the following response.

Senator Harradine requested on 5 June 2002, EWRE Hansard page 282, 'any article in a peer-review journal which describes a cure of a disorder by utilizing human embryonic stem cells.'

In response, the ARC advised that the world-wide web links http://www.nih.gov/news/stemcell/scireport.htm and http://www.nature.com/stemcells/ offer access to background information and lists of peer-reviewed journal papers that provide evidence for the potential uses of human embryonic stem cells.

The ARC also provided references to papers that propose experimental evidence indicating future therapeutic potential (Attachment 1).

In addition to re-supplying this information, the ARC has attached an updated list of references to experimental data using cell cultures and animal models which suggest a worthwhile pathway for experimentation in pursuit of treatments for severe disorders (Attachment 2).

Literature on treatment utilizing adult stem cells

Senator Harradine requested on 5 June 2002, EWRE Hansard page 287, '*a list of articles in peer-reviewed journals which show that adult stem cells have been beneficial in curing or alleviating certain diseases or certain conditions*.'

The ARC provided a list of references to papers outlining the widely accepted use of bone marrow transplants (bone marrow derived adult stem cells) and their use in restoring white blood cells, platelets and immune and clotting protection in patients suffering leukemia and immune deficiencies (Attachment 3).

Attachment 1: Literature citing experimental evidence indicating future therapeutic potential of embryonic stem cells

Bjorklund L.M., Sanchez-Pernaute R, Chung S, Andersson T, Chen IY, McNaught KS, Brownell AL, Jenkins BG, Wahlestedt C, Kim KS, and Isacson O. Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model. Proc. Natl. Acad. Sci. U S A. 2002 Feb 19;99(4):2344-9. PMID: 11782534 [PubMed – indexed for MEDLINE]

Brustle, O., Jones, K.N., Learish, R.D., Karram, K., Choudhary, K., Wiestler, O.D., Duncan, I.D., and McKay, R.D. (1999). Embryonic stem cell-derived glial precursors: a source of myelinating transplants. Science. 285, 754-756.

Buttery, L.D., Bourne, S., Xynos, J.D., Wood, H., Hughes, F.J.,Hughes, S.P., Episkopou, V., and Polak, J.M. (2001). Differentiation of osteoblasts and in vitro bone formation from murine embryonic stem cells. Tissue Eng. 7, 89-99.

Dani, C., Smith, A.G., Dessolin, S., Leroy, P., Staccini, L., Villageois, P., Darimont, C., and Ailhaud, G. (1997). Differentiation of embryonic stem cells into adipocytes in vitro. J. Cell Sci. 110, 1279-1285.

Gill J, Malin M, Hollander GA, and Boyd R (2002). Generation of a complete thymic microenvironment by MTS24 thymic epithelial cells. Nature Immunology, doi: 10.1038/ni812 (advance on-line publication)

Kim, J.H., Auerbach, J.M., Rodríguez-Gómez, J.A., Velasco, I., Gavin, D., Lumelsky, N., Lee, S.H, Nguyen, J., Sánchez-Pernaute, R., Bankiewicz, K., and Mckay, R. (2002) Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease. Nature advance publication, 20 June 2002 (doi 10.1038/nature00900)

Kyba M, Perlingeiro RC, Daley GQ. HoxB4 confers definitive lymphoid-myeloid engraftment potential on embryonic stem cell and yolk sac hematopoietic progenitors. Cell. 2002 Apr 5;109(1):29-37. PMID: 11955444 [PubMed – indexed for MEDLINE]

Lee, S.H., Lumelsky, N., Studer, L., Auerbach, J.M., and McKay, R.D. (2000). Efficient generation of midbrain and hindbrain neurons from mouse embryonic stem cells. Nat. Biotechnol. 18, 675-679.

Liu, S., Qu, Y., Stewart, T.J., Howard, M.J., Chakrabortty, S., Holekamp, T.F., and McDonald, J.W. (2000). Embryonic stem cells differentiate into oligodendrocytes and myelinate in culture and after spinal cord transplantation. Proc. Natl. Acad. Sci. U. S. A. 97, 6126-6131.

Lumelsky, N., Blondel, O., Laeng, P., Velasco, I., Ravin, R., and McKay, R. (2001). Differentiation of Embryonic Stem Cells to Insulin-Secreting Structures Similiar to Pancreatic Islets. Science. 292, 1389-1394.

Maltsev, V.A., Rohwedel, J., Hescheler, J., and Wobus, A.M. (1993). Embryonic stem cells differentiate in vitro into cardiomyocytes representing sinusnodal, atrial and ventricular cell types. Mech. Dev. 44, 41-50.

McDonald JW, Liu XZ, Qu Y, Liu S, Mickey SK, Turetsky D, Gottlieb DI, Choi DW. Transplanted embryonic stem cells survive, differentiate and promote recovery in

injured rat spinal cord. Nat. Med. 1999 Dec;5(12):1410-2. PMID: 10581084 [PubMed – indexed for MEDLINE]

Min JY, Yang Y, Converso KL, Liu L, Huang Q, Morgan JP, Xiao YF. Transplantation of embryonic stem cells improves cardiac function in postinfarcted rats. J. Appl. Physiol. 2002 Jan;92(1):288-96. PMID: 11744672 [PubMed – indexed for MEDLINE]

Potocnik, A.J., Nielsen, P.J., and Eichmann, K. (1994). In vitro generation of lymphoid precursors from embryonic stem cells. EMBO J. 13, 5274-5283.

Rideout WM 3rd, Hochedlinger K, Kyba M, Dalet GQ, Jaenisch R. Correction of a genetic defect by nuclear transplantation and combined cell and gene therapy. Cell 2002 Apr 5;109(1):17-27. PMID: 11955443 [PubMed – indexed for MEDLINE]

Rohwedel, J., Maltsev, V., Bober, E., Arnold, H.H., Hescheler, J., and Wobus, A.M. (1994). Muscle cell differentiation of embryonic stem cells reflects myogenesis in vivo: developmentally regulated expression of myogenic determination genes and functional expression of ionic currents. Dev. Biol. 164, 87-101.

Senior K. Embryonic stem cells used to remylelinate injured rat spinal cord neurons. Lancet. 2000 May 27;355(2918):1890, PMID: 10866454 [PubMed – indexed for MEDLINE]

Strubing, C., Ahnert-Hilger, G., Shan, J., Wiedenmann, B., Hescheler, J., and Wobus, A.M. (1995). Differentiation of pluripotent embryonic stem cells into the neuronal lineage in vitro gives rise to mature inhibitory and excitatory neurons. Mech. Dev. 53, 275-287.

Thomson, J.A. and Marshall, V.S. (1998). Primate embryonic stem cells. Curr. Top. Dev. Biol. 38, 133-165.

Vogel G. Stem cell research. Rat brains respond to embryonic stem cells. Science 2002 Jan 11;295(5553):254-5. PMID: 11786620 [PubMed – indexed for MEDLINE]

Attachment 2: Current literature using cell cultures and animal models which suggest a worthwhile pathway for therapeutic potential of embryonic stem cells

Pluripotency and General Differentiation

Amit, M., Carpenter, M. K., Inokuma, M. S., Chiu, C. P., Harris, C. P., Waknitz, M. A., Itskovitz-Eldor, J. and Thomson, J. A. (2000). Clonally derived human embryonic stem cell lines maintain pluripotency and proliferative potential for prolonged periods of culture. Dev. Biol. 227, 271-8.

Amit, M. and Itskovitz-Eldor, J. (2002). Derivation and spontaneous differentiation of human embryonic stem cells. J. Anat. 200, 225-32.

Draper, J. S., Pigott, C., Thomson, J. A. and Andrews, P. W. (2002). Surface antigens of human embryonic stem cells: changes upon differentiation in culture. J. Anat. 200, 249-58.

Eiges, R., Schuldiner, M., Drukker, M., Yanuka, O., Itskovitz-Eldor, J. and Benvenisty, N. (2001). Establishment of human embryonic stem cell-transfected clones carrying a marker for undifferentiated cells. Curr. Biol. 11, 514-8.

Goldstein, R. S., Drukker, M., Reubinoff, B. E. and Benvenisty, N. (2002). Integration and differentiation of human embryonic stem cells transplanted to the chick embryo. Dev. Dyn. 225, 80-6.

Gropp, M., Itsykson, P., Singer, O., Ben-Hur, T., Reinhartz, E., Galun, E. and Reubinoff, B. E. (2003). Stable genetic modification of human embryonic stem cells by lentiviral vectors. Mol. Ther. 7, 281-7.

Henderson, J. K., Draper, J. S., Baillie, H. S., Fishel, S., Thomson, J. A., Moore, H. and Andrews, P. W. (2002). Preimplantation human embryos and embryonic stem cells show comparable expression of stage-specific embryonic antigens. Stem Cells 20, 329-37.

Itskovitz-Eldor, J., Schuldiner, M., Karsenti, D., Eden, A., Yanuka, O., Amit, M., Soreq, H. and Benvenisty, N. (2000). Differentiation of human embryonic stem cells into embryoid bodies compromising the three embryonic germ layers. Mol. Med. 6, 88-95.

Laslett, A. L., Filipczyk, A. A. and Pera, M. F. (2003). Characterization and culture of human embryonic stem cells. Trends Cardiovasc. Med. 13, 295-301.

Lavik, E., Rogers, A. B., Itskovitz-Eldor, J. and Langer, R. (2003). Differentiation of human embryonic stem cells on three-dimensional polymer scaffolds. Proc. Natl. Acad. Sci. U. S. A. 100, 12741-6.

Levenberg, S., Golub, J. S., Amit, M., Itskovitz-Eldor, J. and Langer, R. (2002). Endothelial cells derived from human embryonic stem cells. Proc. Natl. Acad. Sci. U. S. A. 99, 4391-6.

Ma, Y., Ramezani, A., Lewis, R., Hawley, R. G. and Thomson, J. A. (2003b). High-level sustained transgene expression in human embryonic stem cells using lentiviral vectors. Stem Cells 21, 111-7.

Manuilova, E. S., Arsen'eva, E. L., Khaidarova, N. V., Shugurova, I. M., Gornostaeva, S. N., Inozemtseva, L. S., Katrukha, A. I., Grivennikov, I. A. and Tarantul, V. Z. (2003). [Influence of regulatory genes of type 1 human immunodeficiency virus on proliferation and differentiation of murine embryonic stem cells]. Ontogenez 34, 204-10.

Moore, F. L., Jaruzelska, J., Fox, M. S., Urano, J., Firpo, M. T., Turek, P. J., Dorfman, D. M. and Pera, R. A. (2003). Human Pumilio-2 is expressed in embryonic stem cells and germ cells and interacts with DAZ (Deleted in AZoospermia) and DAZ-like proteins. Proc. Natl. Acad. Sci. U. S. A. 100, 538-43.

Odorico, J. S., Kaufman, D. S. and Thomson, J. A. (2001). Multilineage differentiation from human embryonic stem cell lines. Stem Cells 19, 193-204.

Reubinoff, B. E., Pera, M. F., Fong, C. Y., Trounson, A. and Bongso, A. (2000). Embryonic stem cell lines from human blastocysts: somatic differentiation in vitro. Nat. Biotechnol. 18, 399-404.

Sapienza, C. (2002). Imprinted gene expression, transplantation medicine, and the 'other' human embryonic stem cell. Proc. Natl. Acad. Sci. U. S. A. 99, 10243-5.

Schuldiner, M., Yanuka, O., Itskovitz-Eldor, J., Melton, D. A. and Benvenisty, N. (2000). Effects of eight growth factors on the differentiation of cells derived from human embryonic stem cells. Proc. Natl. Acad. Sci. U. S. A. 97, 11307-12.

Diabetes

Assady, S., Maor, G., Amit, M., Itskovitz-Eldor, J., Skorecki, K. L. and Tzukerman, M. (2001). Insulin production by human embryonic stem cells. Diabetes 50, 1691-7.

Neural differentiation

Carpenter, M. K., Inokuma, M. S., Denham, J., Mujtaba, T., Chiu, C. P. and Rao, M. S. (2001). Enrichment of neurons and neural precursors from human embryonic stem cells. Exp. Neurol. 172, 383-97.

Zhang, S. C., Wernig, M., Duncan, I. D., Brustle, O. and Thomson, J. A. (2001). In vitro differentiation of transplantable neural precursors from human embryonic stem cells. Nat. Biotechnol. 19, 1129-33.

Schuldiner, M., Eiges, R., Eden, A., Yanuka, O., Itskovitz-Eldor, J., Goldstein, R. S. and Benvenisty, N. (2001). Induced neuronal differentiation of human embryonic stem cells. Brain Res. 913, 201-5.

Reubinoff, B. E., Itsykson, P., Turetsky, T., Pera, M. F., Reinhartz, E., Itzik, A. and Ben-Hur, T. (2001a). Neural progenitors from human embryonic stem cells. Nat. Biotechnol. 19, 1134-40.

Blood

Chadwick, K., Wang, L., Li, L., Menendez, P., Murdoch, B., Rouleau, A. and Bhatia, M. (2003). Cytokines and BMP-4 promote hematopoietic differentiation of human embryonic stem cells. Blood 102, 906-15.

Kaufman, D. S., Hanson, E. T., Lewis, R. L., Auerbach, R. and Thomson, J. A. (2001). Hematopoietic colony-forming cells derived from human embryonic stem cells. Proc. Natl. Acad. Sci. U. S. A. 98, 10716-21.

Cardiac regeneration

He, J. Q., Ma, Y., Lee, Y., Thomson, J. A. and Kamp, T. J. (2003). Human embryonic stem cells develop into multiple types of cardiac myocytes: action potential characterization. Circ. Res. 93, 32-9.

Hescheler, J. and Fleischmann, B. K. (2001). Indispensable tools: embryonic stem cells yield insights into the human heart. J. Clin. Invest. 108, 363-4.

Kehat, I., Gepstein, A., Spira, A., Itskovitz-Eldor, J. and Gepstein, L. (2002). High-resolution electrophysiological assessment of human embryonic stem cell-derived cardiomyocytes: a novel in vitro model for the study of conduction. Circ. Res. 91, 659-61.

Kehat, I. and Gepstein, L. (2003). Human embryonic stem cells for myocardial regeneration. Heart Fail. Rev. 8, 229-36.

Kehat, I., Kenyagin-Karsenti, D., Snir, M., Segev, H., Amit, M., Gepstein, A., Livne, E., Binah, O., Itskovitz-Eldor, J. and Gepstein, L. (2001). Human embryonic stem cells can differentiate into myocytes with structural and functional properties of cardiomyocytes. J. Clin. Invest. 108, 407-14.

Lavon, N. and Benvenisty, N. (2003). Differentiation and genetic manipulation of human embryonic stem cells and the analysis of the cardiovascular system. Trends Cardiovasc. Med. 13, 47-52.

Mummery, C., Ward, D., van den Brink, C. E., Bird, S. D., Doevendans, P. A., Opthof, T., Brutel de la Riviere, A., Tertoolen, L., van der Heyden, M. and Pera, M. (2002). Cardiomyocyte differentiation of mouse and human embryonic stem cells. J. Anat. 200, 233-42.

Xu, C., Police, S., Rao, N. and Carpenter, M. K. (2002). Characterization and enrichment of cardiomyocytes derived from human embryonic stem cells. Circ. Res. 91, 501-8.

Law, Science and Ethics

Childress, J. F. (2001). An ethical defense of federal funding for human embryonic stem cell research. Yale J. Health Policy Law Ethics 2, 109, 157-65.

Brivanlou, A. H., Gage, F. H., Jaenisch, R., Jessell, T., Melton, D. and Rossant, J. (2003). Stem cells. Setting standards for human embryonic stem cells. Science 300, 913-6.

Gearhart, J. (1998). New potential for human embryonic stem cells. Science 282, 1061-2.

Kaufman, D. S. (2001). A scientific rationale for human embryonic stem cell research. Yale J. Health Policy Law Ethics 2, 109, 177-87.

Hadjantonakis, A. K. and Papaioannou, V. E. (2002). Can mammalian cloning combined with embryonic stem cell technologies be used to treat human diseases? Genome Biol. 3, REVIEWS1023.

Harris, S. (2002). Asian pragmatism: Japan has set up a legal framework to allow the use and generation of human embryonic stem cell lines. EMBO Rep. 3, 816-7.

Keller, G. and Snodgrass, H. R. (1999). Human embryonic stem cells: the future is now. Nat. Med. 5, 151-2.

Mayor, S. (2001). House of Lords supports human embryonic stem cell research. B.M.G. 322, 189.

McLaren, A. (2002). Human embryonic stem cell lines: socio-legal concerns and therapeutic promise. C. R. Biol. 325, 1009-12.

McWhir, J., Thomson, A. and Sottile, V. (2003). Human embryonic stem cells--realising the potential. Adv. Exp. Med. Biol. 534, 11-25.

Pera, M. F. (2001). Scientific considerations relating to the ethics of the use of human embryonic stem cells in research and medicine. Reprod. Fertil. Dev. 13, 23-9.

Derivation and Growth

Amit, M., Margulets, V., Segev, H., Shariki, K., Laevsky, I., Coleman, R. and Itskovitz-Eldor, J. (2003). Human feeder layers for human embryonic stem cells. Biol. Reprod. 68, 2150-6.

Bongso, A. (1996). Behaviour of human embryos in vitro in the first 14 days: blastocyst transfer and embryonic stem cell production. Clin. Sci. (Lond.) 91, 248-9.

Cheng, L., Hammond, H., Ye, Z., Zhan, X. and Dravid, G. (2003). Human adult marrow cells support prolonged expansion of human embryonic stem cells in culture. Stem Cells 21, 131-42.

Gepstein, L. (2002). Derivation and potential applications of human embryonic stem cells. Circ. Res. 91, 866-76.

Hovatta, O., Mikkola, M., Gertow, K., Stromberg, A. M., Inzunza, J., Hreinsson, J., Rozell, B., Blennow, E., Andang, M. and Ahrlund-Richter, L. (2003). A culture system using human foreskin fibroblasts as feeder cells allows production of human embryonic stem cells. Hum. Reprod. 18, 1404-9.

Lim, J. W. and Bodnar, A. (2002). Proteome analysis of conditioned medium from mouse embryonic fibroblast feeder layers which support the growth of human embryonic stem cells. Proteomics 2, 1187-203.

Ma, L., Tai, H., Li, C., Zhang, Y., Wang, Z. H. and Ji, W. Z. (2003a). Photodynamic inhibitory effects of three perylenequinones on human colorectal carcinoma cell line and primate embryonic stem cell line. World J. Gastroenterol. 9, 485-90.

Mitalipova, M., Calhoun, J., Shin, S., Wininger, D., Schulz, T., Noggle, S., Venable, A., Lyons, I., Robins, A. and Stice, S. (2003). Human embryonic stem cell lines derived from discarded embryos. Stem Cells 21, 521-6.

Pera, M. F., Reubinoff, B. and Trounson, A. (2000). Human embryonic stem cells. J. Cell Sci. 113 (Pt 1), 5-10.

Reubinoff, B. E., Pera, M. F., Vajta, G. and Trounson, A. O. (2001b). Effective cryopreservation of human embryonic stem cells by the open pulled straw vitrification method. Hum. Reprod. 16, 2187-94.

Richards, M., Fong, C. Y., Chan, W. K., Wong, P. C. and Bongso, A. (2002). Human feeders support prolonged undifferentiated growth of human inner cell masses and embryonic stem cells. Nat. Biotechnol. 20, 933-6.

Thomson, J. A., Itskovitz-Eldor, J., Shapiro, S. S., Waknitz, M. A., Swiergiel, J. J., Marshall, V. S. and Jones, J. M. (1998). Embryonic stem cell lines derived from human blastocysts. Science 282, 1145-7.

Thomson, J. A. and Odorico, J. S. (2000). Human embryonic stem cell and embryonic germ cell lines. Trends Biotechnol. 18, 53-7.

Trounson, A. and Pera, M. (2001). Human embryonic stem cells. Fertil. Steril. 76, 660-1.

Trounson, A. O. (2001). The derivation and potential use of human embryonic stem cells. Reprod. Fertil. Dev. 13, 523-32.

Xu, C., Inokuma, M. S., Denham, J., Golds, K., Kundu, P., Gold, J. D. and Carpenter, M. K. (2001). Feeder-free growth of undifferentiated human embryonic stem cells. Nat. Biotechnol. 19, 971-4.

Attachment 3: Literature citing treatment of leukemia and other immune deficiencies utilising adult stem cells

Clift RA and Buckner CD. Marrow transplantation for acute myeloid leukemia. Cancer Invest. 1998;16(1):53-61

Hansen JA, Gooley TA, Martin PJ, et al. Bone marrow transplants from unrelated donors for patients with chronic myeloid leukemia. N. Engl. J. Med. 1998:338(14):962-68

Kernan NA, Bartsch G, Ash RC, et al. Analysis of 462 transplantations from unrelated donors facilitated by the National Marrow Donor Program. N. Engl. J. Med. 1993:328(9):5936-602

Lee SJ, Kuntz KM, Horowitz MM, et al. Unrelated donor bone marrow transplantation for chronic myelogenous leukemia: A decision analysis. Ann. Intern. Med. 1997: 127(12):1080-88

McGlave PB, Shu XO, Wen W, et al. Unrelated donor bone marrow transplantation for chronic myelogenous leukemia: 9 years' experience of the National Marrow Donor Program. Blood 2000;95(7):2219-25

Petersdorf EW, Longton GM, Anasetti C, et al. The significance of HLA-DRB1 matching on clinical outcome after HLA-A, B, DR identical unrelated donor marrow transplantation. Blood 1995;86(4):1606-13.