www.stemcellresearch.org

DO NO HARM
The Coalition of Americans for Research Ethics

1) To advance the development of medical treatments and therapies that do not require the destruction of human life, including the human embryo.

2) To educate and inform public policy makers and the general public regarding these ethically acceptable and medically promising areas of research and treatment.

3) To support continuation of federal laws prohibiting the federal funding of research that requires the destruction of human life, including the human embryo.

1101 Pennsylvania Avenue
Suite 600
Washington, DC 20004
Office: (202) 756-4947
Fax: (202) 756-7523

CURRENT CLINICAL APPLICATIONS OF ADULT STEM CELLS
CANCER TREATMENTS

BRAIN TUMORS

Combination of high-dose chemotherapy with stem cell transplant from the patients themselves shows good response in treatment of brain tumors.

Reference:

1. Dunkel, IJ; "High-dose chemotherapy with autologous stem cell rescue for malignant brain tumors"; Cancer Invest. 18, 492-493; 2000.

"Patients with recurrent medulloblastoma had a significant improvement in long-term survival (median: 34 months) as compared with historical reports; two patients with glioblastoma survive beyond four years without progression."

Reference:

2. Abrey, LE *et al.*; "High dose chemotherapy with autologous stem cell rescue in adults with malignant primary brain tumors"; J. Neurooncol. 44, 147-153; Sept., 1999

"Review of HDCT and stem cell transplant for children with brain tumors. Studies demonstrating durable disease-free survival for a proportion of patients with recurrent malignant gliomas and medulloblastomas/PNET, as well as encouraging data in some of those patients with newly diagnosed brain tumors."

Reference:

3. Finlay, JL; "The role of high-dose chemotherapy and stem cell rescue in the treatment of malignant brain tumors: a reappraisal"; Pediatr. Transplant 3 Suppl. 1, 87-95; 1999

RETINOBLASTOMA

A localized retinoblastoma of the left eye in a 7-year-old girl, was treated by enucleation. She received no additional therapy. Four months later, metastases of retinoblastoma in the lymph nodes, bone and bone marrow were diagnosed. Relapse chemotherapy consisting of three courses of vincristine, cyclophosphamide, etoposide and carboplatin led to a second complete remission. Subsequent high-dose chemotherapy with thiotepa, etoposide and carboplatin and autologous stem

cell transplantation with CD34-selected stem cells were successful, with no adverse effects. No radiotherapy was given and the girl remains in continuous second remission with a follow-up of more than 4 years.

Reference:

4. Hertzberg H *et al.*; "Recurrent disseminated retinoblastoma in a 7-year-old girl treated successfully by high-dose chemotherapy and CD34-selected autologous peripheral blood stem cell transplantation"; Bone Marrow Transplant 27(6), 653-655; March 2001

Patients with metastatic retinoblastoma have a poor prognosis with conventional treatments. This study used intensive conventional chemotherapy, high-dose chemotherapy, with autologous stem cell rescue, and radiation therapy. The treatment strategy was effective for all four patients with metastatic retinoblatoma that does not involve the central nervous system, surviving event free from 46-80 months after diagnosis.

Reference:

5. Dunkel IJ *et al.*; "Successful treatment of metastatic retinoblastoma"; Cancer 89, 2117-2121; Nov 15 2000

OVARIAN CANCER

Report studying whether patients benefit more from autologous stem cell transplantation. "Some patients with ovarian cancer seem to have good outcomes after autotransplantation".

Reference:

6. Stiff PJ *et al.*; "High-dose chemotherapy and autologous stem-cell transplantation for ovarian cancer: An autologous blood and marrow transplant registry report"; Ann. Intern. Med. 133, 504-515; Oct. 3, 2000

"Developing data suggest that this approach in both of these settings merit further evaluation for the treatment of epithelial ovarian carcinoma." Used autologous, purified peripheral blood stem cells

Reference:

7. Schilder, RJ and Shea, TC; "Multiple cycles of high-dose chemotherapy for ovarian cancer"; Semin. Oncol. 25, 349-355; June 1998

SOLID TUMORS

**Merkel cell carcinoma is a rare cutaneous tumor with neuroendocrine differentiation; there is no standard protocol for treatment of the metastatic disease. This study used high-dose chemotherapy and autologous peripheral blood stem cell transplantation to achieve complete remission that lasted for 6 months.

Reference:

8. Waldmann V *et al.*; "Transient complete remission of metastasized merkel cell carcinoma by highdose polychemotherapy and autologous peripheral blood stem cell transplantation"; Br. J. Dermatol. 143, 837-839; Oct 2000

**Patients with metastatic or locally advanced, unresectable soft tissue sarcoma are seldom curable, with 5-year survival rates of less than 10%. Used high-dose chemotherapy with autologous hematopoietic stem cell transplant; "a high survival rate was observed in HDCT-treated patients who were in complete remission after conventional chemotherapy."

Reference:

9. Blay JY *et al.*; "High-dose chemotherapy with autologous hematopoietic stem-cell transplantation for advanced soft tissue sarcoma in adults"; J. Clin. Oncol. 18, 3643-3650; Nov 1 2000

"The prognosis of metastatic malignant mesenchymal tumors (MMT) remains poor." Used high-dose chemotherapy with bone marrow or peripheral blood stem cell transplant. "A response exceeding 50% was observed in 6/18 patients (response rate 33%)."

Reference:

10. Lafay-Cousin L *et al.*; "High-dose thiotepa and hematopoietic stem cell transplantation in pediatric malignant mesenchymal tumors: a phase II study"; Bone Marrow Transplant 26, 627-632; Sept. 2000

High-dose chemotherapy followed by autologous haematopoietic rescue is widely used in the treatment of patients with paediatric malignancies. It is now well established as a major component for the treatment of children with metastatic neuroblastoma over the age of one at diagnosis. Its place for other tumours, such as metastatic Ewing and rhabdomyosarcoma, needs to be better established."

Reference:

11. Michon, J and Schleiermacher, G. "Autologous haematopoietic stem cell transplantation for paediatric solid tumors", Baillieres Best Practice Research in Clinical Haematology 12, 247-259, March-June, 1999.

Used for malignant solid tumors. Overall response rate 96%, complete clinical response rate 67%. Treatment described as safe, feasible, and active.

Reference:

12. Schilder, RJ *et al.*; "Phase I trial of multiple cycles of high-dose chemotherapy supported by autologous peripheral-blood stem cells"; J. Clin. Oncol. 17, 2198-2207; July 1999

TESTICULAR CANCER

"Thirty-seven (57%) of the 65 patients are continuously disease-free. Three additional patients are disease-free with subsequent surgery. High-dose chemotherapy was associated with significant morbidity but no treatment-related mortality. High-dose chemotherapy as initial salvage chemotherapy achieved impressive long-term survival with acceptable toxicity in patients with relapsed testicular cancer."

Reference:

13. Bhatia S *et al.*; "High-dose chemotherapy as initial salvage chemotherapy in patients with relapsed testicular cancer"; J. Clin. Oncol. 18, 3346-3351; Oct. 19, 2000

"High-dose chemotherapy with the transplantation of peripheral blood stem cells (PBSC) has been performed for the treatment of advanced testicular cancer patients." "After mobilization of peripheral blood stem cells with G-CSF alone, sufficient amounts of MNC were obtained from testicular cancer patients who had undergone chemotherapy several times."

Reference:

14. Hanazawa, K *et al.*; "Collection of peripheral blood stem cells with granulocyte-colonystimulating factor alone in testicular cancer patients"; Int. J. Urol. 7, 77-82; March 2000.

MULTIPLE MYELOMA, LEUKEMIAS

UMBILICAL CORD BLOOD EFFECTIVE AT TREATING ADULT BLOOD DISORDERS

A new report shows that umbilical cord blood can provide effective treatment of various blood disorders in adults. It had previously been assumed that there were too few stem cells in cord blood to treat adults, and only children were treated. The results of this study show that cord blood stem cells can proliferate extensively and provide sufficient numbers of cells for adult treatments.

Reference:

15. Laughlin MJ *et al.*; "Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors", New England Journal of Medicine 344, 1815-1822; June 14, 2001

This retrospective study included 21 children with acute lymphoblastic leukaemia, 15 with acute myelogenous leukaemia and one each with chronic myelogenous leukaemia, refractory anaemia with myelodysplastic syndrome (MDS) and juvenile myelomonocytic leukaemia (JMML). These data confirm that HLA-mismatched, unrelated CBT is a feasible procedure to cure a significant proportion of children with leukaemia, especially if conducted in a favourable phase of the disease.

Reference:

16. Ohnuma K *et al.*; "Cord blood transplantation from HLA-mismatched unrelated donors as a treatment for children with haematological malignancies"; Br J Haematol 112(4), 981-987; March 2001

a lymphoproliferative disorder with abnormalities characteristic of malignant T cell lymphoma (angioimmunoblastic T cell lymphoma -- -year old male
patient with unusually aggressive AILD, At relapse, treatment with high dose chemotherapy shown to be successful. The patient is alive and diseaseafter
APSCT. Considering the poor prognosis of the majority of patients with AILD, intensive

Reference:

17. Lindahl J ; "Highhemolysing
AILD"; Leuk Res 25(3), 267- 1
Patients given highblood
stem cells rather than bone marrow results in higher rates of overall and diseaseand
restores blood counts faster. Patients in whom the benefit of peripheral blood cells was most apparent were those with advanced hematologic cancer. Other studies have also shown that the use -blood cells is associated with fewer days of hospitalization and lower overall costs.

Reference:

. Bensinger WI ; "Transplantation of bone marrow as compared with peripheralfrom
HLAMedicine
344, 175-
ng stem cell transplantation. The authors note that "Stem cell
transplantation has been successfully used to treat a wide variety of hematologic malignancies. New ul in
overcoming tumor resistance."

Reference:

Margolis J *et al.*
Semin. Oncol. 27, 524-
apeutic approach in
patients with acute myelocytic leukemia over 60 years of age."

Reference:

Gorin NC *et al.*
acut myelocytic leukaemia in patients over 60 years of age: importance of the source of stem
-893; Sept 2000
"Infants with acute leukemia have a poor prognosis when treated with conventional chemotherapy."
-year overall survival 64%. "SCT is a valid option in the treatment of inf
may overcome the high risk of relapse with conventional chemotherapy showing very reduced toxicity."

Reference:

Marco F *et al.* -Dose
-C -3261; Sept. 15 2000
Updated June 25, 2001 Cancer Treatments with Adult Stem Cells David A. Prentice
5
"Actuarial survival and disease-free survival at 34 months are 56% and 50% respectively, with 95% confidence interval (25-78%).These results suggest that nonmyeloablative conditioning significantly reduces transplant-related toxicity, thus making a second transplant feasible."

Reference:

22. Nagler A *et al.*; "Second allogeneic stem cell transplantation using nonmyeloablative conditioning for patients who relapsed or developed secondary malignancies following autologous transplantation"; Exp. Hematol. 28, 1096-1104, Sept. 1, 2000
Review of autologous stem cell treatment strategies. "Controlled clinical trials have demonstrated a long-term disease-free survival of 40%-50% for patients treated with at least two courses of HIDAC. Other studies have demonstrated that postremission autologous bone marrow transplantation results in a disease-free survival equal to or better than conventional chemotherapy. However, autotransplantation with mobilized peripheral blood stem cells (PBSC) would now be preferred instead of autologous bone marrow, due to the shorter hematopoietic reconstitution period."

Reference:

23. Bruserud O *et al.*; "New strategies in the treatment of acute myelogenous leukemia: mobilization and transplantation of autologous peripheral blood stem cells in adult patients"; Stem Cells 18, 343-351; 2000

Study to evaluate high-dose melphalan followed by autologous stem-cell transplantation in patients with refractory multiple myeloma. High-dose therapy with melphalan 200 mg/m(2) is feasible with high response rates (58% overall) and an OS of 19 months in patients with refractory multiple myeloma."

Reference:

24. Vesole, DH *et al*.; "High-Dose Melphalan With Autotransplantation for Refractory Multiple Myeloma: Results of a Southwest Oncology Group Phase II Trial"; J Clin Oncol 17, 2173-2179; July 1999.

BREAST CANCER

**The "data suggest that high-dose chemotherapy with hematopoietic stem cell rescue is safe and can be beneficial to patients with high-risk primary breast cancer and for those with metastatic breast cancer achieving complete response/no evidence of disease."

Reference:

25. Damon LE *et al.*; "High-dose chemotherapy and hematopoietic stem cell rescue for breast cancer: experience in California"; Biol. Blood Marrow Transplant 6, 496-505; 2000

Stem cells in circulating blood can be isolated, expanded in number in culture, and provide better clinical results.

Reference:

26. Paquette, RL *et al*., "Ex vivo expanded unselected peripheral blood: progenitor cells reduce posttransplantation neutropenia, thrombocytopenia, and anemia in patients with breast cancer", Blood 96, 2385-2390; October, 2000.

Updated June 25, 2001 Cancer Treatments with Adult Stem Cells David A. Prentice 6

"The collection of small aliquots of bone marrow (BM), followed by ex vivo expansion for autologous transplantation may be less morbid, and more cost-effective, than typical BM or blood stem cell harvesting. Passive elimination of contaminating tumor cells during expansion could reduce reinoculation risks." "It is feasible to perform autotransplants solely with BM cells grown ex vivo in perfusion bioreactors from a small aliquot." this procedure could reduce the risk of tumor cell reinoculation with autotransplants and may be valuable in settings in which small stem cell doses are available, eg, cord blood transplants."

Reference:

27. Stiff P *et al*.; "Autologous transplantation of ex vivo expanded bone marrow cells grown from small aliquots after high-dose chemotherapy for breast cancer"; Blood 95, 2169-2174; March 15, 2000

"This report is the first describing infusion of autologous MSCs with therapeutic intent. We found that autologous MSC infusion at the time of PBPC transplantation is feasible and safe. The observed rapid hematopoietic recovery suggests that MSC infusion after myeloablative therapy may have a positive impact on hematopoiesis and should be tested in randomized trials."

Reference:

28. Koc, ON *et al*.; "Rapid Hematopoietic Recovery After Coinfusion of Autologous-Blood Stem Cells and Culture-Expanded Marrow Mesenchymal Stem Cells in Advanced Breast Cancer Patients Receiving High-Dose Chemotherapy"; J Clin Oncol 18, 307-316; January 2000

NEUROBLASTOMA

"According to initial reports, stage 4 neuroblastoma patients with amplification of the MYCN protooncogene developed progressive disease within 8 months. The prognosis for such patients, however, should now be reevaluated in light of recent results achieved with up-to-date combination chemotherapy. Not all patients with advanced neuroblastoma who have more than 10 copies of MYCN will die. The requisites for survival in such patients seem to be intensive induction

chemotherapy, effective surgery, irradiation, and the use of SCT" (stem cell transplant).

Reference:

29. Kawa, K *et al.*; "Long-Term Survivors of Advanced Neuroblastoma With MYCN Amplification: A Report of 19 Patients Surviving Disease-Free for More Than 66 Months"; J Clin Oncol 17:3216-3220; October 1999

NON-HODGKIN'S LYMPHOMA

"To determine differences in prognosis between primary progressive Hodgkin's disease (HD) and aggressive non-Hodgkin's lymphoma (NHL), we retrospectively analyzed patients with progressive lymphoma who were treated with different salvage chemotherapy regimens including high-dose chemotherapy (HDCT) followed by autologous stem-cell support (ASCT). There are striking differences in the prognosis of patients with progressive HD and aggressive NHL. The prognosis of progressive NHL patients is dismal. Most patients have rapidly progressive disease after salvage treatment and are, therefore, excluded from HDCT programs. In contrast, progressive HD patients can achieve long-term survival after HDCT."

Reference:

30. Josting, A; "Treatment of Primary Progressive Hodgkin's and Aggressive Non-Hodgkin's Lymphoma: Is There a Chance for Cure?"; J Clin Oncol 18, 332-339; 2000

"Patient achieved complete remission and has survived in continuous complete remission for more than 72 months to date. Marrow-ablative chemotherapy facilitated by PBSCT is thought to be useful as part of the primary therapy for patients with NHL who have poorer prognoses."

Reference:

31. Kirita T *et al.*; "Primary non-Hodgkin's lymphoma of the mandible treated with radiotherapy, chemotherapy, and autologous peripheral blood stem cell transplantation"; Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 90, 450-455; Oct. 2000

"These results suggest first that ex vivo expansion of hematopoietic stem cells in patients with non-Hodgkin's lymphoma is feasible without incurring the parallel risk of amplifying tumor cells; second, that Flt3-L did not stimulate the growth of tumor cells while it clearly favored the growth of normal progenitors."

Reference:

32. Yao M *et al.*; "Ex vivo expansion of CD34-positive peripheral blood progenitor cells from patients with non-Hodgkin's lymphoma: no evidence of concomitant expansion of contaminating bcl2/JH-positive lymphoma cells"; Bone Marrow Transplant 26, 497-503; Sept. 2000

RENAL CELL CARCINOMA

"Nonmyeloablative allogeneic stem-cell transplantation can induce sustained regression of metastatic renal-cell carcinoma in patients who have had no response to conventional immunotherapy."

Reference:

33. Childs R *et al.*, "Regression of Metastatic Renal-Cell Carcinoma after Nonmyeloablative Allogeneic Peripheral-Blood Stem-Cell Transplantation", New England Journal of Medicine 343, 750-758; Sept. 14, 2000

"The complete regression of metastatic disease, which has now been maintained for more than 1 year, is compatible with a graft-versus-tumor effect."

Reference:

34. Childs, RW; "Successful Treatment of Metastatic Renal Cell Carcinoma With a Nonmyeloablative Allogeneic Peripheral-Blood Progenitor-Cell Transplant: Evidence for a Graft-Versus-Tumor Effect:; J Clin Oncol 17, 2044-2049; July 1999

Autoimmune diseases

–multiple sclerosis, systemic lupus erythematosus, juvenile rheumatoid arthritis, rheumatoid arthritis

High-dose chemotherapy followed by autologous HSCT is feasible and safe, and can result in longterm improvement of disease activity in patients whose condition previously did not respond to conventional antirheumatic drugs or TNF blocking agents. The persistence of active disease in some patients may reflect the heterogeneity of the underlying disease process.

Reference:

35. Verburg RJ *et al.*; "High-dose chemotherapy and autologous hematopoietic stem cell transplantation in patients with rheumatoid arthritis: results of an open study to assess feasibility, safety, and efficacy"; Arthritis Rheum 44(4), 754-760; April 2001

Reference:

36. Wulffraat NM *et al.*; "Prolonged remission without treatment after autologous stem cell transplantation for refractory childhood systemic lupus erythematosus"; Arthritis Rheum 44(3), 728-731; March 2001

** "Autoimmune diseases that are resistant to conventional treatment cause severe morbidity and even mortality. In the present study we demonstrate that complete remissions can be achieved in refractory polychondritis and systemic lupus erythematosus (SLE), even at advanced stage, with the use of autologous stem-cell transplantation (SCT). Remissions persisted after reconstitution of the immune system. In the treatment of advanced systemic sclerosis (SSc), stable disease may be achieved with autologous SCT."

Reference:

37. Rosen O *et al.*; "Autologous stem-cell transplantation in refractory autoimmune diseases after in vivo immunoablation and ex vivo depletion of mononuclear cells"; Arthritis res. 2, 327-336; 2000

Nineteen patients (14 female, 5 male) with severe autoimmune diseases were treated. Nine had a rheumatologic disorder (5 juvenile chronic arthritis, 1 rheumatoid arthritis, 1 systemic vasculitis, 1 Sjogren's syndrome, 1 Behct's disease), 4 a neurologic disorder (3 multiple sclerosis, 1 myasthenia), 3 a haematologic disease (2 pure red cell aplasia, 1 autoimmune thrombocytopenia), 2 had a gastrointestinal disease (1 Crohn's disease, 1 autoimmune enteropathy) and 1 had a multiple autoimmune disorder. There was no regimen-related toxicity and no opportunistic infections occurred. Ninety percent of the patients improved and/or had a complete remission after the procedure. Fifty percent of the subjects went into complete or partial remission after a median followup of 15 months. A non-myeloablative conditioning regimen was able to induce persistent remission in some patients with severe autoimmune diseases. There was no mortality or morbidity related to the procedure. The extent of remission remains to be established.

Reference:

38. Rabusin M *et al.*; "Immunoablation followed by autologous hematopoietic stem cell infusion for the treatment of severe autoimmune disease"; Haematologica 85(11 Suppl), 81-85; Nov. 2000

**Study that supports the concept that patients with autoimmune cytopenias with severe resistant disease might be appropriate candidates for autologous stem cell transplantation.

Reference:

39. Papadaki HA *et al.*; "Assessment of bone marrow stem cell reserve and function and stromal cell function in patients with autoimmune cytopenias"; Blood 96, 3272-3275; Nov 1 2000

Patients (including several children) with severe lupus were treated with their own bone marrow stem cells, and had relief of symptoms, with little or no need for medication after treatment.

References

40. Traynor AE *et al.*; "Treatment of severe systemic lupus erythematosus with high-dose chemotherapy and haemopoietic stem-cell transplantation: a phase I study"; Lancet 356, 701-707; August 26, 2000

Numerous studies showing efficacy of adult stem cell transplants in the successful treatment of autoimmune diseases.

References:

41. Burt, RK and Traynor, AE; "Hematopoietic Stem Cell Transplantation: A New Therapy for Autoimmune Disease"; Stem Cells17, 366-372; 1999
Overview—juvenile rheumatoid arthritis; multiple sclerosis; rheumatoid arthritis; systemic lupus erythematosus.
42. Burt RK *et al*.; "Hematopoietic stem cell transplantation of multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus"; Cancer Treat. Res. 101, 157-184; 1999
43. Traynor A and Burt RK; "Haematopoietic stem cell transplantation for active systemic lupus erythematosus"; Rheumatology 38, 767-772; August 1999
44. Martini A *et al*.; "Marked and sustained improvement 2 years after autologous stem cell transplant in a girl with system sclerosis"; Rheumatology 38, 773; August 1999
45. Hawkey CJ *et al*.; "Stem cell transplantation for inflammatory bowel disease: practical and ethical issues"; Gut 46, 869-872; June 2000
46. Burt, RK *et al*., "Autologous hematopoietic stem cell transplantation in refractory rheumatoid arthritis: sustained response in two of four patients", Arthritis & Rheumatology 42, 2281-2285, November, 1999.
47. Burt, R.K. *et al*., "Gene-marked autologous hematopoietic stem cell transplantation of autoimmune disease", Journal of Clinical Immunology 20, 1-9; January 2000.

Stroke

A cultured stem cell line (originally derived from an adult tumor; a "teratocarcinoma", sometimes called an "embryonal carcinoma" because it mimics some of the characteristics of embryonic cells.) The cultured and adapted cell line was used in successful treatment of several stroke patients.

Reference

48. Kondziolka D *et al*.; "Transplantation of cultured human neuronal cells for patients with stroke"; Neurology 55, 565-569; August 2000

Immunodeficiencies

Banked unrelated umbilical cord blood was used to reconstitute the immune system in 2 brothers with X-linked lymphoproliferative syndrome and 1 boy with X-linked hyperimmunoglobulin-M syndrome. Two years after transplantation, all 3 patients have normal immune systems. These reports support the wider use of banked partially matched cord blood for transplantation in primary immunodeficiencies.

Reference:

49. Ziegner UH *et al.*; "Unrelated umbilical cord stem cell transplantation for X-linked immunodeficiencies"; J Pediatr 138(4), 570-573; April 2001
Eight children with severe immunodeficiencies treated by adult bone marrow stem cell transplants. Six of 8 showed relatively normal immune systems after 1 year.

Reference

50. Amrolia, P. *et al.*, "Nonmyeloablative stem cell transplantation for congenital immunodeficiencies", Blood 96, 1239-1246, Aug. 15, 2000.

Anemias

Allogeneic peripheral blood stem cell transplantation (PBSCT) is rarely applied for the treatment of severe aplastic anemia (SAA) because of questionable durability of engraftment and increased risk of graft versus host disease (GVHD). We performed allogeneic PBSCT in 3 SAA patients from their human leukocyte antigen (HLA)-identical siblings. In 2 cases, no graft failure has been observed, and a successful and complete hematological recovery was achieved and maintained for 28 and 25 months, respectively. In conclusion, PBSCT provides a quick and complete hematological recovery in SAA patients.

Reference:

51. Gurman G *et al.*; "Allogeneic peripheral blood stem cell transplantation for severe aplastic anemia"; Ther Apher 5(1), 54-57; Feb. 2001

Results suggest that treatment can reverse progression of vasculopathy. Bone marrow transplantation may enable stenoses to heal and can substantially reduce cranial blood velocity, suggesting that allogeneic bone marrow transplantation may prevent infarction or brain damage.

Reference:

52. Steen RG *et al.*; "Improved cerebrovascular patency following therapy in patients with sickle cell disease: initial results in 4 patients who received HLA-identical hematopoietic stem cell allografts"; Ann Neurol 49(2), 222-229; Feb. 2001

Able to treat severe anemias using transplants of adult bone marrow stem cells.

References

53. Gonzalez MI *et al.*; "Allogeneic peripheral stem cell transplantation in a case of hereditary sideroblastic anaemia"; British Journal of Haematology 109, 658-660; 2000

54. Kook H *et al.*; "Rubella-associated aplastic anemia treated by syngeneic stem cell transplantations"; Am. J. Hematol. 64, 303-305; August 2000

Possibility of using adult stem cell transplantation as cure for sickle cell anemia.

Reference

55. Wethers DL; "Sickle cell disease in childhood: Part II. Diagnosis and treatment of major complications and recent advances in treatment"; Am. Fam. Physician 62, 1309-1314; Sept. 15, 2000

Successful treatment of a congenital thrombocytopenia using allogeneic peripheral blood stem cell transplantation.

Reference

56. Yesilipek *et al.*; "Peripheral stem cell transplantation in a child with amegakaryocytic thrombocytopenia"; Bone Marrow Transplant 26, 571-572; Sept. 2000

Chronic Viral Infection With Complications

57. Fujii N *et al.*; "Allogeneic peripheral blood stem cell transplantation for the treatment of chronic active epstein-barr virus infection"; Bone Marrow Transplant 26, 805-808; Oct. 2000

58. Okamura T *et al.*; "Blood stem-cell transplantation for chronic active Epstein-Barr virus with lymphoproliferation"; Lancet 356, 223-224; July 2000

Cartilage and Bone Diseases

59. Biopsies removed from 57 patients considered for cartilage transplantation were grown. Explant cultures allowed cell number expansion. Fifty-four out of 57 biopsies grew cells. Fanning out of the cells began after 5-15 days in culture. Two passages later, cell numbers in the 10(7) range were achieved. Explants of articular chondrocytes cultured in vitro consistently yield monolayer cultures. The cells appear to revert to dedifferentiated chondrocytes, expressing a mesenchymal stem cell protein profile. Simultaneously, these cells regained their capacity to proliferate.

Reference:

60. Robinson D *et al.*; "Characteristics of cartilage biopsies used for autologous chondrocytes transplantation"; Cell Transplant 10(2), 203-208; 2001 Mar-Apr

61. Horwitz, EM *et al.*; "Transplantability and therapeutic effects of bone marrow-derived mesenchymal cells in children with osteogenesis imperfecta"; Nat. Med. 5, 309-313; March 1999.

Corneal scarring

Fifteen of 16 eyes (93.7%) achieved epithelialization with a mean time to epithelial healing of 15.2

days. The only eye that failed to heal was subsequently diagnosed with total limbal stem cell deficiency. Visual acuity improved in five of nine (44%) sighted eyes. No patient experienced any major surgical or medical complication after the procedure. Amniotic membrane transplantation represents a safe and effective method to restore a stable corneal epithelium in eyes after primary surgical removal of band keratopathy arising from ocular causes.

Reference:

62. Adnerson DF *et al.*; "Amniotic Membrane Transplantation After the Primary Surgical Management of Band Keratopathy"; Cornea 20(4), 354-361; May 2001

Amniotic membrane transplantation appears to be a safe and effective method of restoring a stable corneal epithelium for cases of partial limbal stem cell deficiency and can be considered as an alternative to limbal autograft or allograft. 17 eyes of 15 patients; All eyes exhibited a stable, intact corneal epithelial surface after a mean follow up period of 25.8 months with no eyes developing recurrent erosion or persistent epithelial defect. The mean time to re-epithelialisation was 22.8 days. Overall improvement in visual acuity was observed in 92.9% of 14 eyes with visual potential.

Reference:

63. Anderson DF *et al.*; "Amniotic membrane transplantation for partial limbal stem cell deficiency"; Br J Ophthalmol 85(5), 567-575; May 2001

An objective long term benefit from the procedure (improved Snellen acuity, reduced frequency of epithelial defects, reduced vascularisation, and scarring) was recorded for four out of five patients. Some subjective benefit was also reported. However, in no instances were donor cells recovered from the ocular surface at 3-5 years post-graft. Initial experiments to examine sensitivity indicated that any surviving donor cells must have constituted less than 2.5% of cells sampled. Limbal stem cell allotransplantation can provide long term benefits, as measured by objective criteria. However, such benefits do not necessarily correlate with survival of measurable numbers of donor cells on the ocular surface.

Reference:

64. Henderson TR *et al.*; "The long term outcome of limbal allografts: the search for surviving cells"; Br J Ophthalmol 85(5), 604-609; May 2001

**Adult stem cells from relatives used to restore vision

Nine living related donors, 8 recipients (10 eyes, various conditions). Restoration of corneal epithelium, opacification reduced, visual improvement; 2 initial failures.

Reference:

65. Daya SM, Ilari FA; "Living related conjuctival limbal allograft for the treatment of stem cell deficiency"; Opthalmology 180, 126-133; January 2001

Updated June 25, 2001 Other Clinical Uses of Adult Stem Cells David A. Prentice

13

Adult Stem Cells Used to Grow New Corneas

Researchers in the United States and Taiwan have used corneal adult stem cells to grow new corneas for patients with previously untreatable eye damage. Adult stem cells were taken from the patients themselves in 16 cases, or a family member for 4 other patients. The cells were then grown in culture before transplantation onto the damaged eyes. Sixteen of the 20 patients had improved vision. Dr. Ivan Schwab, professor of ophthalmology at the University of California at Davis Medical School, leader of the U.S. team, said "We think this is the beginning of a very exciting change in terms of how we manage surface disease of many kinds, not just in the eye."

References

66. Schwab IR *et al.*; "Successful transplantation of bioengineered tissue replacements in patients with ocular surface disease"; Cornea 19, 421-426; July 2000.

67. Tsai *et al.*; "Reconstruction of damaged corneas by transplantation of autologous limbal epithelial cells."; New England Journal of Medicine 343, 86-93, 2000.

68. Tsubota K *et al.*; "Treatment of severe ocular-surface disorders with corneal epithelial stem-cell transplantation"; New England Journal of Medicine 340, 1697-1703; June 3, 1999

Blood and Liver Disease

**4-month-old girl received stem cell transplant after receiving living-related liver transplant from same donor (mother). Four months after stem cell transplant the patient was disease-free, complete donor chimerism in bone marrow and stable hepatic function without any immunosuppressive therapy.

Reference

69. Matthes-Martin S *et al*.; "Successful stem cell transplantation following orthotopic liver transplantation from the same haploidentical family donor in a girl with hemophagocytic lymphohistiocytosis"; Blood 96, 3997-3999; Dec 1, 2000

**Primary amyloidosis is a plasma cell disorder in which deposits of amyloid protein cause progressive organ failure; most common target is the kidney, although heart, liver, and nervous tissue effects are also seen. Compared to standard treatments, high-dose chemotherapy with autologous peripheral blood stem cell transplantation is shown to be much more effective in the clinical condition of patients.

Reference:

70. Sezer O *et al*.; "Novel approaches to the treatment of primary amyloidosis"; Exper Opin. Investig. Drugs 9, 2343-2350; Oct 2000

Gene Therapy

*****First successful trial of human therapy, re-injecting the infants' own bone marrow stem cells containing a normal copy of the gene that they lacked.

Reference:

71. Cavazzana-Calvo M *et al*.; "Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease"; Science 288, 669-672; April 28, 2000

Heart Damage

First successful human stem cell treatment for heart disease uses adult stem cells

The first reports of successful treatment for heart disease using the patient's own adult muscle stem cells are encouraging news regarding therapy after heart attack. French physicians implanted skeletal muscle stem cells back into the patient; the encouraging result after eight months' follow-up underlines the potential of this new approach using adult stem cells. Further clinical trials are now underway in Europe and the U.S. for other patients with heart disease. No embryonic stem cells have ever been reported to be used in human trials.

A review of potential heart treatments notes that cell transplantation is a potential therapeutic approach for patients with chronic heart failure. Experimental transplantation of muscle cells showed that the grafted cells can functionally integrate with and augment the function of the recipient heart. The scientists note that skeletal stem cells are abundant and can be grafted successfully into the animal's own heart even after genetic manipulation in vitro.

References:

72. Menasché P *et al.* "Myoblast transplantation for heart failure." *Lancet* 357, 279-280; Jan 27, 2001
73. Menasché P *et al.* ["Autologous skeletal myoblast transplantation for cardiac insufficiency. First clinical case."] [article in French] *Arch Mal Coeur Vaiss* 94(3), 180-182; March 2001
74. "Doctor Puts Arm Muscle Cells Into Patient's Heart", Associated Press, May 30, 2001
75. "First Percutaneous Endovascular Case of Heart Muscle Regeneration Completed with Bioheart's MyoCell(TM) Product", PRNewswire, May 30, 2001.
76. El Oakley RM *et al.*; "Myocyte transplantation for cardiac repair: A few good cells can mend a broken heart"; *Annals of Thoracic Surgery* 71, 1724 –1733; 2001

General References Related to Clinical Uses of Adult Stem

Cells

Recent studies have revealed that much of this remarkable developmental potential of embryonic stem cells is retained by small populations of cells within most tissues in the adult. Intercellular signals that control the proliferation, differentiation and survival of stem cells are being identified and include a diverse array of growth factors, cytokines and cell adhesion molecules. Intracellular mechanisms that regulate stem cell fate are also emerging and include established second messenger pathways, novel transcription factors and telomerase. The possibility that a decline in the numbers or plasticity of stem cell populations contributes to aging and age-related disease is suggested by recent findings. The remarkable plasticity of stem cells suggests that endogenous or transplanted stem cells can be 'tweaked' in ways that will allow them to replace lost or dysfunctional cell populations in diseases ranging from neurodegenerative and hematopoietic disorders to diabetes and cardiovascular disease.

Reference:

77. Rao MS and Mattson MP; "Stem cells and aging: expanding the possibilities"; Mech Ageing Dev 122(7), 713-734; May 31, 2001

Mesenchymal stem cells (MSCs) are the first non-hematopoietic progenitors to be isolated from the bone marrow and extensively characterized. In addition to their ability to support hematopoiesis, MSCs can differentiate into osteocytes, chondrocytes, tenocytes, adipocytes and smooth muscle cells. This article will review our current understanding of bone marrow stroma and MSCs and their potential therapeutic role in the setting of hematopoietic stem cell transplantation.

Reference:

78. Koc ON and Lazarus HM; "Mesenchymal stem cells: heading into the clinic"; Bone Marrow Transplant 27(3), 235-239; Feb. 2001

It appears that basal haematopoiesis is maintained throughout life, yet, the capacity to cope with haematological stress is decreased in advanced age. In principle, stem cells derived from aged donors can be used for autologous transplantation, when needed to recover basic haematopoiesis. Current methods for expansion and maintenance of stem cells in vitro enable examination of stem cell potential for long-term expansion and function. Understanding of the mechanisms underlying these processes will enable the fidelity of stem cell expansion and maintenance of their potential for long-term function.

Reference:

79. Globerson A; "Haematopoietic stem cell ageing"; Novartis Found Symp 235, 85-96; discussion 96-100, 101-4; 2001

This study examined whether cryopreservation following expansion has a detrimental effect on the ability of cells to engraft, using the NOD-SCID mouse model. Cord blood (CB) CD34(+) cells were incubated for 7 days with stem cell factor (SCF), flt-3 ligand (FL), and megakaryocyte growth and development factor (MGDF). Expanded CD34(+) cells were transplanted into NOD-SCID mice either fresh or following cryopreservation and thawing. Thawed expanded CD34(+) cells had significantly higher SCID Engrafting

Potential (SEP) than freshly expanded CD34(+) cells. Results suggest that prior cryopreservation does not prevent expanded cells engrafting in NOD-SCID mice.

Reference:

80. Rice AM *et al.*; "Prior cryopreservation of ex vivo-expanded cord blood cells is not detrimental to engraftment as measured in the nod-scid mouse model"; J Hematother Stem Cell Res 0(1), 157-165; Feb. 2001

Represents the first case of successful transplantation of PBSC, cryopreserved twice and purged after cryopreservation. Indicates that purging procedures can successfully be carried out with cryopreserved cell material and that purified CD34+ cells can be cryopreserved a second time before transplantation, without affecting their hematopoietic capacity.

Reference:

81. Humpe A *et al.*; "Successful transplantation and engraftment of peripheral blood stem cells after cryopreservation, positive and negative purging procedures, and a second cryopreservation cycle"; Ann Hematol 80(2), 109-112; Feb. 2001

General review of growth factors using in hematopoietic stem cell transplants. Recently, EPO has been shown to significantly accelerate hematopoietic reconstitution after peripheral blood stem cell transplantation (PBSCT) resulting in reduced infection rates. Both, G-CSF and GM-CSF have been shown, in numerous trials, to shorten the period of chemotherapy-induced neutropenia, with reduction in attendant morbidity and to mobilize PBSC. In addition, administration of both cytokines after PBSCT significantly reduced the use of antibiotics and duration of hospitalization suggesting an economic benefit.

Reference:

82. Dempke W *et al.*; "Human hematopoietic growth factors: old lessons and new perspectives"; Anticancer Res 20(6D), 5155-5164; 2000 Nov-Dec

Review of increasing use of umbilical cord blood for transplants; banking of cells, etc.

Reference:

83. Surbek DV and Holzgreve W; "Fetal cells from cord blood as stem cell source: current status and possible implications in gynaecologic oncology"; Eur J Gynaecol Oncol 22(1), 6-12; 2001

Mobilized peripheral blood progenitor cells (PBSC) are increasingly being used instead of bone marrow for allogeneic transplantation. This article gives a concise and clinically oriented overview on current results and perspectives of allogeneic peripheral blood stem cell transplantation, with particular focus on reconstitution of hematopoiesis and the immune system, graft-versus-host disease, graft-versus-leukemia effects, intensityreduced conditioning, and graft engineering.

Reference:

84. Dreger P and Schmitz N; "Allogeneic transplantation of blood stem cells: coming of age?"; Ann Hematol 80(3), 127-136; March 2001

**Previously reported human stem cell frequencies and their in vivo self-renewal activity have been markedly underestimated.

Reference

85. Cashman JD and Eaves CJ; "High marrow seeding efficiency of human lymphomyeloid repopulating cells in irradiated NOD/SCID mice"; Blood 96, 3979-3981; Dec. 1 2000

Updated June 25, 2001 Other Clinical Uses of Adult Stem Cells David A. Prentice 18

**Evidence for expansion protocol to maintain cord blood stem cells for clinical applications.

Reference

86. Kobari L *et al.;* "In vitro and in vivo evidence for the long-term multilineage (myeloid, B, NK, and T) reconstitution capacity of ex vivo expanded human CD34(+) cord blood cells"; Exp Hematol 28, 1470-1480, December 2000

Updated June 25, 2001 Other Clinical Uses of Adult Stem Cells David A. Prentice 19

**Study notes that disease recurrence is lower after peripheral blood stem cell transplants than with bone marrow; "The general opinion is that peripheral blood grafts are indicated

for patients with advanced disease, whereas for patients with early-phase disease the two sources may give comparable results."

Reference:

87. Bacigalupo A *et al.*; "Bone marrow or peripheral blood as a source of stem cells for allogeneic transplants"; Curr. Opin. Hematol. 7, 343-347; Nov 2000

**Quality of life for 415 adult patients who received hematopoietic stem cell transplants was measured; typical patients can look forward to a quality of life after transplantation that is broadly comparable to that of the normal population.

Reference:

88. Bush NE *et al.*; "Conditional and unconditional estimation of multidimensional quality of life after hematopoietic stem cell transplantation: a longitudinal followup of 415 patients"; Biol. Blood Marrow Transplant 6, 576-591; 2000

**Review of techniques to mobilize hematopoietic bone marrow stem cells into peripheral blood.

Reference:

89. Fu S, Liesveld J; "Mobilization of hematopoietic stem cells"; Blood Rev 14, 205-218; Dec 2000

**Technique to expand numbers of human hematopoietic stem cells in culture. Cells from umbilical cord blood and adult patient peripheral blood were expanded with 2 factors, flt-3 ligand and thrombopoietin/c-mpl ligand, and maintained for prolonged periods (up to 16 weeks), and sufficient numbers were generated for adult transplantation.

Reference:

90. Gilmore GL *et al.*; "Ex vivo expansion of human umbilical cord blood and peripheral blood CD34(+) hematopoietic stem cells"; Exp. Hematol. 28, 1297-1305; Nov 1 2000

**Review of records for cord blood stem cell transplants. Results showed survival comparable to bone marrow transplants. "This large registry study confirms the potential benefit of using umbilical cord blood hematopoietic stem cells for allogeneic transplants."

Reference:

91. Gluckman E; "Current status of umbilical cord blood hematopoietic stem cell transplantation"; Exp. Hematol. 28, 1197-1205; Nov 1 2000

Review of potentials for stem cell transplantation.

Reference

92. Steward CG; "Stem cell transplantation for non-malignant disorders"; Baillieres Best Pract. Res. Clin. Haematol. 13, 343-363; Sept. 2000

93. Slavin S; "new strategies for bone marrow transplantation"; Curr. Opin. Immunol. 12, 542-551; Oct. 2000

Improved technique to quickly expand numbers of cord blood cells in culture, allowing adequate numbers for treatment of adult patients.

Reference:

94. McNiece I *et al.*; "Increased expansion and differentiation of cord blood products using a two-step expansion culture"; Exp. Hematol. 28, 1181-1186; Oct. 2000

"Can expand primitive hematopoietic progenitors from Cord Blood and Peripheral Blood and expanded cells retain the capacity for myeloid and lymphoid differentiation. These findings emphasize the importance of assessing multi-lineage differentiation capacity following ex-vivo expansion.

Reference:

95. Lewis ID, Verfaillie CM; "Multi-lineage expansion potential of primitive hematopoietic progenitors. Superiority of umbilical cord blood compared to mobilized peripheral blood"; Exp. Hematol. 28, 1087-1095; Sept. 1, 2000
Generating a high frequency of clonally repopulating stem cells from blood.
Reference
96. Cho RH, Muller-Sieburg CE; "High frequency of long-term culture-initiating cells retain in vivo repopulation and self-renewal capacity"; Exp. Hematol. 28, 1080-1086; Sept. 1, 2000
97. Jacobs P *et al.*; "Allogeneic stem cell transplantation. An economic comparison of bone marrow, peripheral blood, and cord blood technologies"; Int. J. Technol. Assess Health Care 16, 874-884; Summer 2000
Autologous (same patient) circulating blood stem cell transplants show faster recovery, less transplant problems, shorter hospital stay, and reduced cost compared to bone marrow transplants.
Reference
98. "Overview of autologous stem cell transplantation", Saba, N *et al*., Critical Reviews of Oncology and Hematology 36, 27-48, October 2000.
Allogeneic peripheral blood stem cell transplants as good or better than bone marrow
Reference
99. Ringden O *et al.*, "Peripheral blood stem cell transplantation from unrelated donors: a comparison with marrow transplantation", Blood 94, 455; July 15, 1999
Reviews of current protocols allowing better methods for collection of stem cells from peripheral blood.
References
100. Hester J; "Peripheral blood stem cell collection: the interaction of technology, procedure, and biological factors"; Transfus. Sci. 23, 125-132; Oct. 2000
101. Kessinger A; "Collection of autologous peripheral blood stem cells in steady state"; Baillieres Best Pract. Res. Clin. Haematol. 12, 19-26; Mar-Jun, 1999
102. Korbling M; "In vivo expansion of the circulating stem cell pool"; Stem Cells 16 Suppl 1, 131-138; 1998.
103. Kessinger A, Sharp JG; "Mobilization of blood stem cells"; Stem Cells 16 Suppl 1, 139-143; 1998
Review of cord blood stem cell transplants
Reference
Updated June 25, 2001 Other Clinical Uses of Adult Stem Cells David A. Prentice
22
104. Huhn RD; "Umbilical cord blood stem cell transplantation and banking"; N J Med 97, 53-57; Sept. 2000
105. **"Bibliography. Current world literature. Hematopoietic stem cell transplantation"; Curr. Opin. Hematol. 7, B171-189; Nov 2000