Abstracts on studies conducted with transfer factors from blood leukocytes

Biotherapy 1996;9(1-3):175-85

In vitro studies during long-term oral administration of specific transfer factor.

Pizza G, De Vinci C, Fornarola V, Palareti A, Baricordi O, Viza D.

Immunodiagnosis and Immunotherapy Unit, S. Orsola Malpighi Hospital, Bologna, Italy.

153 patients suffering from recurrent pathologies, i.e. viral infections (keratitis, keratouveitis, genital and labial herpes) uveitis, cystitis, and candidiasis were treated with in vitro produced transfer factor (TF) specific for HSV-1/2, CMV and Candida albicans. The cell-mediated immunity of seropositive patients to HSV-1/2 and/or CMV viruses was assessed using the leucocyte migration inhibition test (LMT) and lymphocyte stimulation test (LST) in presence of the corresponding antigens, and the frequency of positive tests before, during and after TF administration was studied. The data were stratified per type of test, antigen and the recipients' pathology, and statistically evaluated. For the LMT, a total of 960 tests were carried out for each antigen dilution, 3 different antigen dilutions were used per test. 240/960 tests (25.4%) were found positive during non-treatment or treatment with unspecific TF, whereas 147/346 tests (42.5%) were found positive when the antigen corresponding to the specificity of the TF administered to the patient was used (P < 0.001). When the data were stratified following pathology, a significant increased incidence of positive tests during specific treatment was also observed (0.0001 < P < 0.05). In the LST (1174 tests), a significant increase of thymidine uptake was observed in the absence of antigen (control cultures), during treatment with both specific and unspecific TF, but also in the presence of antigen and/or autologous serum during specific TF administration (P < 0.0001). TF administration also significantly increased the soluble HLA class I antigens level in 40 patients studied to this effect.

Publication Types:
Clinical trial

Biotherapy 1996;9(1-3):123-32

A preliminary report on the use of transfer factor for treating stage D3 hormone-unresponsive metastatic prostate cancer.


Immunodiagnosis and Immunotherapy Unit, S. Orsola-Malpighi Hospital, Bologna, Italy.

As conventional treatments are unsuccessful, the survival rate of stage D3 prostate cancer patients is poor. Reports have suggested the existence of humoral and cell-mediated immunity (CMI) against prostate cancer tumour-associated antigens (TAA). These observations prompted us to treat stage D3 prostate cancer patients with an in vitro produced transfer factor (TF) able to transfer, in vitro and in vivo, CMI against bladder and prostate TAA. Fifty patients entered this study and received one intramuscular
injection of 2-5 units of specific TF monthly. Follow-up, ranging from 1 to 9 years, showed that complete remission was achieved in 2 patients, partial remission in 6, and no progression of metastatic disease in 14. The median survival was 126 weeks, higher than the survival rates reported in the literature for patients of the same stage.

Publication Types:
Clinical trial

Transfer factor as an adjuvant to non-small cell lung cancer (NSCLC) therapy.


Istituto di Clinica Chirurgica II, S. Orsola-Malpighi, Bologna, Italy.

The rationale for using transfer factor (TF) in lung cancer patients is that the possibility of improving their cell-mediated immunity to tumour associated antigens (TAA) may improve their survival. From Jan 1984 to Jan 1995, 99 non-small cell lung cancer (NSCLC) resected patients were monthly treated with TF, extracted from the lymphocytes of blood bank donors. In the same period, 257 NSCLC resected patients were considered as non-treated controls. The survival rates of the TF treated group appear significantly improved both for patients in stages 3a and 3b, and patients with histological subtype "large cell carcinoma" (P < 0.02). Survival of TF treated patients is also significantly higher (P < 0.02) for patients with lymph node involvement (N2 disease). The results of this study suggest that the administration of TF to NSCLC resected patients may improve survival.

Publication Types:
Clinical trial
Controlled clinical trial

Transfer factor with anti-EBV activity as an adjuvant therapy for nasopharyngeal carcinoma: a pilot study.


University of Malaya, Kuala Lumpur, Malaysia.

Overall survival of nasopharyngeal carcinoma (NPC) at UICC stage IV still remains unsatisfactory even with combination chemotherapy (CT) and radio-therapy (RT). In view of the association of reactivation of Epstein-Barr virus (EBV) with the development and recurrence of NPC, immunotherapy in the form of transfer factor (TF) with specific activity against EBV (TF-B1) was suggested as an adjuvant to a combination of CT and RT in order to improve survival. In the present study, 6 UICC stage IV patients received TF-B1 and another 6 patients matched for disease stage were given TF prepared from
peripheral blood leucocytes (TF-PBL). Results were compared with another 18 patients matched by age, sex, and stage of disease who received standard therapy without TF during the same period (C group). After a median follow up of 47.5 months, the survival for the TF-B1 group was found to be significantly better ($P = < 0.05$) than the PBL and C group. While the 8 patients with distant metastasis (DM), not treated with TF-B1 (6 in the control and 2 in the PBL group), died due to progressive disease (average survival being 14.3 months), both patients with DM in the TF-B1 group had complete remission: one died of tuberculosis after surviving for 3.5 years and another is still alive, disease free, after 4.2 years. Although the series involved a small number of cases, the apparent effect of adjuvant immunotherapy in the form of TF with anti-EBV activity is of considerable interest.

Publication Types:

Clinical trial

Biotherapy 1994;8(1):63-8

**Transfer factor prevents relapses in herpes keratitis patients: a pilot study.**

Pizza G, Meduri R, De Vinci C, Scorolli L, Viza D.

Immunodiagnosis and Immunotherapy Unit, S. Orsola-Malpighi Hospital, Bologna, Italy.

Transfer Factor is a dialysable moiety obtained from immune lymphocytes. It has been successfully used for the treatment of several viral infections including labial and genital herpes. In the present study, thirty-three patients with low immune response to HSV antigens and suffering from herpes ocular infections were orally treated with HSV-specific transfer factor (TF). Their relapse index was reduced from 20.1 before treatment to 0.51 after TF administration, with only 6/33 patients relapsing. Although this is not a placebo-controlled-randomized study, the results suggest that TF specific for HSV antigens may be efficacious for preventing relapses of ocular herpes infections as has been the case with genital and labial localisations.

Publication Types:

Clinical trial

Arch Esp Urol 1989;42 Suppl 2:191-6

**Immunotherapy with transfer factor in hormone-resistant metastasized carcinoma of the prostate.**

[Article in Spanish]

Corrado F, Pizza G, de Vinci C, Corrado G.

Fifty-six patients with metastatic hormone-resistant carcinoma of prostate (stage D3) were submitted to immunotherapy with a monthly intramuscular injection of predominantly specific transfer factor (TF) produced in vitro. Patient follow-up ranging from 1 to 8 years revealed completed remission was achieved in one patient, partial remission in 6, and there was no progression of the metastatic disease in 14

**Transfer factor for the treatment of HBsAg-positive chronic active hepatitis.**


Transfer factor was obtained from four patients having recovered from acute type-B viral hepatitis. It was replicated in vitro using the LDV/7 lymphoblastoid cell line. This in vitro-produced transfer factor specific for hepatitis B (TFdL-H) was administered to 10 randomly selected patients with biochemically and histologically proven HBsAg-positive chronic active hepatitis (CAH) at 15-day intervals over a 6-month period. In three out of four initially HBeAg-positive patients, anti-HBe antibodies appeared when the HBeAg disappeared. In one of these patients and in two other HBsAg-positive patients, the appearance of anti-HBs antibodies was noted. The improvement in several biochemical parameters of the TFdL-H patients was statistically significant when compared with those of another group of 10 randomly selected untreated CAH patients. Liver biopsies in six out of eight treated patients showed a histological improvement at the end of the treatment. These results suggest that TFdL-H may be used with beneficial effect for the treatment of HBsAg-positive CAH.

Publication Types:

Clinical trial

Lymphokine Res 1985 Fall;4(4):351-7

**Transfer of reactivity with in vitro produced transfer factor in rhesus and owl monkeys.**


Transfer factors against two heterologous antigens, Herpesvirus saimiri and owl monkey kidney cells, were replicated in vitro in a human lymphoblastoid cell line (LDV/7) and injected into rhesus and owl monkeys. Transfer of immunity was demonstrated by the leukocyte migration inhibition assay. This study suggests that heterologous transfer factor, replicated in vitro, can transfer cellular immunity against membrane antigens in rhesus and owl monkeys.


**Serial in vitro transfer of hypersensitivity to cancer antigens by sensitised lymphocytes.**

**Fazio M, Carnevale-Schianca F, Sabidussi A.**

Chair of Medical Oncology, University of Turin, Italy.
An account is given of the experimental serial in vitro transfer of antigen-specific delayed hypersensitivity to peripheral leukocytes, using antigen-specific Transfer factor solely as the initial source. Transfer was assessed with the leukocyte migration, lymphocyte locomotion and leukocyte adherence inhibition tests. The positive test results observed in all the experiments suggest that Transfer factor does not act as such, but triggers a reaction that expands the effect of hypersensitivity.

PMID: 8710398 [PubMed - indexed for MEDLINE]

JAMA 1987 Feb 6;257(5):651-5

**Augmentation of skin test reactivity and lymphocyte blastogenesis in patients with AIDS treated with transfer factor.**


Nine patients with the acquired immunodeficiency syndrome (AIDS) were administered four doses of pooled transfer factor obtained from the lymphocytes of three healthy controls and three homosexuals with stable lymphadenopathy and serum antibody to the human immunodeficiency virus. Before receiving transfer factor, all patients exhibited anergy to skin test antigens. After four weeks of transfer factor therapy, six of seven patients tested had at least one skin test response. Lymphocyte blastogenic responses to phytohemagglutinin rose from a stimulation index of 6.77 +/- 1.31 before treatment to 19.77 +/- 6.24 after four weeks of transfer factor therapy. Smaller but significant increases were also seen in blastogenic responses to antigens. Improvements in immune responses diminished after administration of transfer factor was halted. Thus, administration of transfer factor to patients with AIDS resulted in partial immune reconstitution. Further studies are indicated to examine the clinical efficacy of this immune response modifier in the treatment of AIDS.


**Guidelines for immunotherapy of antigen-specific defects with transfer factor.**

Wilson GB, Fudenberg HH, Keller RH.

Dialyzable leukocyte extracts (DLE) containing transfer factor (TF) with documented specificity for one or more microbial antigens have shown previously variable clinical effectiveness in treating many infectious diseases caused by viruses, fungi, protozoa and mycobacteria. The efficacy has sometimes been strong, and at other times dubious, in treating patients with inherited or presumably "acquired" immunodeficiency diseases refractory to standard therapy. The recent development of assays for screening leukocyte donors of DLE, for monitoring recipients, and especially for determining the potency of various DLE preparations containing antigen-specific TF and for predicting the clinical course of disease have, in our hands, greatly improved the likelihood of successful immunotherapy with TF. Two representative cases are reported, one involving a patient with an antigen selective defect to Candida, and another involving a patient with an antigen selective defect to Mycobacterium fortuitum. Both patients responded as judged by laboratory tests and clinical improvement when treated with certain DLE preparations but not with others. Finally, certain DLE preparations appeared to suppress cell-mediated immunity in vivo and this suppression could be predicted by in vitro tests. Based on these results, guidelines for optimal therapy with DLE are proffered.
Transfer factor--a lymphocyte cell surface component.

Schroder I, Luneburg S.

An attempt was made to locate the biologically active component of the DLE in lymphocytes. The test was based on the recovery of sheep cell-rosetting capacity in trypsinized human lymphocytes (recovery assay). Comparisons of the extract from trypsinized leukocytes and the leukocyte supernatant (after trypsinization) yielded the following results: The peptide fraction detached from the cell surface by trypsin (30 min with 0.5 g trypsin/l at 37 degrees C) accounts for most of the TF activity of the whole lymphocytes. Of the two TF activities (fractions II and III), fraction III obviously stems from the cell interior because it cannot be liberated by trypsin. Fraction III is characterized by an unusually high UV absorption quotient (A 260/280), probably due to a large nucleotide content. Trypsination leads to the biologically active TF fraction going into the supernatant. Fraction II consists almost entirely of cell surface peptides. It is relatively easy to separate it cleanly, and it has a high level of biological activity (1 microgram/ml is still detectable).

Leukocyte migration inhibition of buffy coats from patients with autoimmune thrombocytopenic purpura when exposed to normal platelets: modulation by transfer factor.

Borkowsky W, Karpatkin S.

Cellular-mediated immunity was studied in autoimmune thrombocytopenic purpura (ATP) patients by investigating leukocyte migration inhibition (LMI) following the interaction of normal platelets with patients' lymphocytes. When normal platelets were incubated with leukocyte buffy coats of ATP patients, the migration index (MI) was significantly impaired compared to buffy coats from normal subjects, employing 4 different concentrations of platelets. At the highest platelet concentration (10(9)/ml), MI was 0.87 +/- 0.04 (SEM) for ATP lymphocytes compared to 1.05 +/- 0.05 (p less than 0.01) for normal lymphocytes. Nine of 21 patients had an MI less than 0.80, whereas all control subjects had MIs greater than 0.85. Similar results were obtained at 2 different platelet membrane concentrations. At 500 micrograms/ml, the MI for ATP lymphocytes was 0.74 +/- 0.04, compared to 0.98 +/- 0.08 (p less than 0.01) for normal lymphocytes (12 experiments). An inverse relationship was noted between platelet count and lymphokine production in ATP patients (r = 0.815, p less than 0.001, 10 experiments). Transfer factor from an ATP patient in remission converted an abnormal LMI response of 0.68 +/- 0.04 from a patient with severe thrombocytopenia to 0.84 +/- 0.07 (p less than 0.005, 8 experiments). Similar results were obtained with transfer factor from 2 other patients in remission. Transfer factor from a patient with severe thrombocytopenia converted a normal response of 1.04 +/- 0.05 of normal subjects to a lower response of 0.88 +/- 0.04 (p less than 0.03, 12 experiments). Thus, lymphocytes of ATP patients are primed to recognize and be perturbed by normal platelets, whereas normal lymphocytes are not. This indicates specificity of the antigen-lymphocyte reaction in ATP patients. Transfer factor is capable of modulating this response in vitro.
Transfer factor in restoration of cell mediated immunity in lung cancer patients.

Fujisawa T, Yamaguchi Y, Kimura H.

We studied the transfer factor (TF) with regard to in vivo and in vitro restoration of cell mediated immunity (CMI) in lung cancer patients. Twenty-eight lung cancer patients who had undergone resection were the recipients and 30 household contact family members with a positive reactivity to lung cancer extract were the donors of TF. Immunologic status was evaluated by delayed type cutaneous hypersensitivity (DTH), peripheral T lymphocyte number, PHA lymphocyte blastogenesis, serum blocking activity (SBA) and leucocyte adherence inhibition (LAI) test. When TF was administered twice subcutaneously to the patients, there was a statistically significant restoration or augmentation of DTH, PHA lymphocyte blastogenesis and abrogation of SBA, particularly in patients with suppressed CMI. These results suggest that it was the TF obtained from relatives of lung cancer patients with positive reactivity to tumor associated antigens restored or augmented tumor specific and nonspecific CMI in these lung cancer patients.

Biotherapy 1996;9(1-3):143-7

Dialysable lymphocyte extract (DLyE) in infantile onset autism: a pilot study.

Fudenberg HH.

Neurolmmuno Therapeutics Research Foundation Spartanburg, S.C., USA.

40 infantile autistic patients were studied. They ranged from 6 years to 15 years of age at entry. 22 were cases of classical infantile autism; whereas 18 lacked one or more clinical defects associated with infantile autism ("pseudo-autism"). Of the 22 with classic autism, 21 responded to transfer factor (TF) treatment by gaining at least 2 points in symptoms severity score average (SSSA); and 10 became normal in that they were main-streamed in school and clinical characteristics were fully normalized. Of the 18 remaining, 4 responded to TF, some to other therapies. After cessation of TF therapy, 5 in the autistic group and 3 of the pseudo-autistic group regressed, but they did not drop as low as baseline levels.

Publication Types:

Clinical trial


Serial in vitro transfer of hypersensitivity to cancer antigens by sensitised lymphocytes.

Fazio M, Carnevale-Schianca F, Sabidussi A.

Chair of Medical Oncology, University of Turin, Italy.

An account is given of the experimental serial in vitro transfer of antigen-specific delayed hypersensitivity to peripheral leukocytes, using antigen-specific Transfer factor solely as the initial source. Transfer was assessed with the leukocyte migration, lymphocyte locomotion and leukocyte adherence inhibition tests.
The positive test results observed in all the experiments suggest that Transfer factor does not act as such, but triggers a reaction that expands the effect of hypersensitivity.

Arch Intern Med 1981 Mar;141(4):533-7

**Transfer factor therapy for histoplasmosis in a patient with Hodgkin's disease.**

Catanzaro A, Spitler LE, Campbell GD, Moser KM.

A patient with recurrent chronic histoplasmosis was diagnosed also as having Hodgkin's disease. Studies of cell-mediated immunity (CMI) demonstrated no reaction to histoplasmin by skin test, lymphocyte transformation (LT), or leukocyte inhibition factor (LIF) assay. Clinical and immunologic studies were performed during treatment with 19 doses of dialyzable transfer factor (TF) prepared from a normal donor with strong CMI against histoplasmin. Transfer of CMI to the patient was demonstrated by all three tests. All tests reverted to nonreactive during the period of observation. Repeated doses of dialyzable TF were followed by reconversion of skin tests. The LIF assay was most reactive. Reactivation of histoplasmosis occurred during antimetabolic therapy for Hodgkin's disease; however, the lesions cleared rapidly when TF was added to amphotericin B. Amphotericin B was administered at a dosage of 25 mg three times each week during the entire study.

Thymus 1981 Feb;2(4-5):257-6

**Effects of dialyzable leukocyte extracts with transfer factor activity on leukocyte migration in vitro.**

V. Antigen-specific lymphocyte responsiveness can be initiated by two structurally distinct polyribonucleopeptides.

Wilson GB, Paddock GV, Fudenberg HH.

Human transfer factors (TF) active in specifically inducing responsiveness in human thymus-derived (T) lymphocytes previously nonresponsive to purified protein derivative from Mycobacterium tuberculosis (PPD) or to Coccidioides immites (Cocci) in vitro were isolated from the dialyzable portion of extracts of immune leukocytes (DLE). Each TF segregated into two active fractions after high-pressure reverse-phase liquid chromatography (HPLC), suggesting the presence of two TF components in DLE for each antigen specificity. Determination of the structures of both TF components specific for PPD was accomplished by evaluating their activity after incubation with various endonucleases, exonucleases, phosphatases, peptidases and a protease. The results indicated that both PPD-specific TF components are oligoribonucleopeptides but that they are structurally distinct. Simplest-case molecular models were constructed on the basis of the data obtained.

Am J Obstet Gynecol 1978 Mar 1;130(5):572-84

**Transfer factor and possible applications in gynecology.**

Freedman RS, Wharton JT, Rutledge F, Sinkovics JG.

Dialyzable transfer factor (TFd) is reviewed against its historical background, preparation methods, physiochemical properties, possible mechanisms of action, pharmacology, and clinical studies, including
several areas relating to gynecology. The possible role of TFd as an adjunct in the treatment of cancer is discussed. The discussion centers on gynecologic cancer in several patients who have received TFd. The difficulties and future possibilities for this modality of treatment are considered.

Publication Types:
Review

Laryngoscope 1978 Jan;88(1 Pt 2 Suppl 8):79-82

Transference of cell mediated immunity in patients with head and neck cancer.

Vetto RM, Burger DR.

A group of 67 patients with head and neck cancer has been studied of which 40 have received immunologic transfer factor from a normal donor pool. Examination of these patients revealed that lymphocyte reactivity to nonspecific mitogens is depressed in patients who have head and neck cancer to a much greater extent than is seen in patients with other types of tumors. Furthermore, the depression is more prevalent among patients who have been treated with radiation. Patients in the head and neck group who have received transfer factor show an initial decreased response to PHA stimulation in culture. This is not seen in a control group of head and neck cancer patients or in patients with nonsquamous cancer. Thymus-derived lymphocytes are depressed in patients with head and neck cancer, irrespective of whether they have received radiation. Th T-lymphocyte levels increased in eight of 38 patients who received nonimmune transfer factor, but 7 of these were in the group who had not received radiation. The leukocyte adherence inhibition (LAI) test has been used to determine tumor immunity in the patient test group. Changes in tumor immunity did not occur in those patients who received normal nonimmune transfer factor. Studies are presently in progress which provide for treatment of patients with head and neck cancer with specific squamous carcinoma immune transfer factor.

Med Clin North Am 1976 May;60(3):585-90

Transfer factor: a potential agent for cancer therapy.

LoBuglio AF, Neidhart JA.

This review has attempted to describe the characteristics of transfer factor which make it a very attractive potential agent for immunotherapy. Preliminary observations suggest that it may be capable of modifying resistance to a variety of diseases including cancer but considerable progress in basic knowledge regarding this agent is crucial to its successful application in clinical disease states. Fortunately, a sizable number of interested and dedicated investigators are exploring these difficult problems and their success may lead to new approaches in immunotherapy.

Publication Types:
Review
Properties and activities of transfer factor.

Kirkpatrick CH.

Although there is agreement that transfer factor endows skin test-negative subjects with the ability to develop the delayed allergic responses of the transfer factor donors, there is little direct information on the mechanism of this phenomenon or on the nature of the active components (s). This report reviews some of the known effects of transfer factor or immune responses and inflammation. It is concluded that transfer factor has multiple sites of action, including effects on the thymus, on lymphocyte-monocyte and/or lymphocyte-lymphocyte interactions, as well as direct effects on cells in inflammatory sites. It is also suggested that the "specificity" of transfer factor is determined by the immunologic status of the recipient rather than by informational molecules in the dialysates. Finally, it is proposed that many effects of transfer factor may be due to changes in intracellular cyclic nucleotide content, especially accumulation of cGMP, in immunologically reactive cells.

Transfer factor II: results of therapy.

Spitler LE, Levin AS, Fudenberg HH.

Transfer factor is a dialyzable extract of sensitized leukocytes, which transfers reactivity from skin test-positive donors to skin test-negative recipients. Transfer factor supplied by our laboratory has been used therapeutically to induce cellular immunity in 78 patients around the world. Many patients received multiple doses of transfer factor ranging from 1 unit given every 6 months for 3 years to 1 unit every week for 6 months to as much as 8 units per week for a brief period. A total of 299 units of transfer factor have been given. Diseases in which transfer factor appeared to cause improvement include the Wiskott-Aldrich syndrome, severe combined immunodeficiency disease, mucocutaneous candidiasis, chronic active hepatitis, coccidioidomycosis, dysgammaglobulinemia, Behcet disease, aphthous stomatitis, linear morphea, familial keratoacanthoma and malignancy.

Transfer factor therapy: evidence for nonspecificity.

Ballow M, Dupont B, Hansen JA, Good RA.

Four patients were treated with multiple doses of dialyzed transfer factor in which one Wiskott-Aldrich patient with abnormal IgG monocyte receptors obtained benefit. All patients converted skin reactivity, and had improved in vitro lymphocyte responses to varying degrees. Three patients developed positive reactivity to allogeneic cells in MLC, and one patient developed DNBC reactivity. These latter two findings suggest transfer factor may act by inducing a nonspecific maturation of lymphocyte function. A possible mechanism for the action of transfer factor is discussed.
We have detected new clues to the composition and function of "Transfer Factor" using the direct Leucocyte Migration Inhibition (LMI) test as an in vitro assay of Dialysates of Leucocyte Extracts (DLE). This approach has revealed two opposing antigen-specific activities to be present in the same > 3500 < 12,000 DA dialysis fraction - one activity is possessed of Inducer/Helper function (Inducer Factor). The opposing activity is possessed of Suppressor function (Suppressor Factor). When non-immune leucocyte populations are cultured with Inducer Factor they acquire the capacity to respond to specific antigen and inhibition of migration occurs. This conversion to reactivity is antigen-specific and dose-dependent. When immune leucocyte populations are cultured with Suppressor Factor their response to specific antigen is blocked and Inhibition of Migration is prevented.