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RESEARCH ARTICLE

# Transfer Factors or Dialyzable leukocyte Extracts as Immunomodulating Peptides: A Conceptual Review on Broad Spectrum of Therapeutic Areas, Immunologic and Clinical Responses, Trends and Perspectives

***Dina Tulina*, Mike KS Chan, Michele WBF and Shing Yi Pan***

*Stellar Biomolecular Research, Germany*

***Corresponding author:** *Dina Tulina, Stellar Biomolecular Research, 205 Klosterstrasse, 67480, Edenkoben, Germany*

## Abstract

Immune Modulating Peptides (IMP) discussed in literature as a universal immunocorrectors with wide areas of usage which balance the immune system without causing global immune suppression or overreaction. The present article aim is to review the effect and drawbacks of IMPs in form of Dialyzable leukocyte Extracts (DLE) or Transfer Factors (TF) during and following chemotherapy, radiotherapy, drugs interactions, cancer response and clinical outcomes in different cases of cancers such as metastatic breast cancer, glioma, prostate cancer, osteosarcoma and others. The considered cases of immune overreaction and IMP's impact include autoimmune diseases such as rheumatoid arthritis, multiple sclerosis and allergic reactions. The most difficult therapeutic decision is to choose the right treatment for patients with cancer and autoimmune diseases as they both attempt to supervise and control the immune system, managing immune cells in opposite sides. As patients with autoimmune disease experience difficulty to stay in such treatment when immune cells stimulated in order to identify and destroy cancer cells the IMP as immunocorrectors become one of the main and only healthy choices. The universal mechanism of IMPs action and the absence of contraindications extend the indications for their use in pediatric practice. This includes the complex treatment of respiratory viral infections, the possibility of using in frequently ill children with clinical signs of immune dysfunction and acute intestinal infections. According to the reports on safety, absence of adverse and side effects along with positive outcome for patients the IMPs considered as valuable immunocorrector.

## Keywords

Immune modulating peptides, Immune regulation, Transfer factor, Dialyzable leukocyte extracts

## Abbreviations

IMP: Immune Modulating Peptides, TF: Transfer Factor; DLE: Dialyzable leukocyte Extracts; NK: Natural Killer Cells; IL: Interleukin; HIV: Human Immunodeficiency Virus; TNF-α - Tumor Necrosis Factor Alpha; IFN-γ: Interferon Gamma IFN-g; RANTES: Regulated on Activation, Normal T Cell Expressed and Secreted; hBD-2: Human Beta Defensin 2

## Introduction

Immune Modulating Peptides (IMP) are exceptional specific inhibitors of protein-protein interactions and, hence, are beneficial modulators of protein-mediated signaling of immune system. IMP's effect based on reinstating immune balance without causing global immune suppression or overreaction. Technology uses specific peptides with certain properties and abilities to stimulate an antigen-specific expansion of regulatory T cells - leading mediators of immune tolerance. These cells are qualified to suppress autoantigen-specific helper T cells, which release proinflammatory cytokines and are reliable for immune pathology in autoimmune diseases. Transfer factors (TF) include both Inducer fractions and Regulator fractions - historically called "suppressor fractions". Inducer fractions transport an apparently mature immune response from donor to recipient. Regulator fractions help control overreactions and limit allergies and autoimmune conditions. Inducer fractions strengthen antigenic stimulus, which induces production of IFN-γ, IL- 2 and TNF-α by CD4+Th1 cells

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[1]. As result, cell-mediated immune response develops against target antigen [2], and it comprises interleukins (IL-6 and IL-8) produced by activated monocytes [3,4]. Particular factors that decrease cell mediated immunity, Th2 supremacy are age, immunodeficiency, cytotoxic cancer treatments, chronical stress, metastatic diseases, environment, etc. Suppressor fractions control and regulate immune response to an antigen and stimulating IL-10 formation and inhibitory cytokines by Th2 cells [5,6]. The adjuvant-like TF components have a non-specific activity expressed by enhancing immune response to other antigens or allergens [7].

The present article aim is to review the effect and drawbacks of IMPs in form of Dialyzable leukocyte Extracts (DLE) or Transfer Factors (TF) during and following chemotherapy, radiotherapy, drugs interactions, cancer response and clinical outcomes in different cases of cancers such as metastatic breast cancer, glioma, prostate cancer, osteosarcoma and others.

Current anticancer therapy tactics include surgery, radiotherapy or chemotherapy which confirmed improvement of disease prognosis and has increased survival. In patients with breast cancer, antineoplastic chemotherapy has improved overall clinical outcome. Anyway, various side effects linked with chemotherapy and radiotherapy. It is clear that side effects, not only affect tumour, but also target bone marrow activity and divide lymphocytes causing lymphocytopenia [8] which may induce subsequent clinical immunodeficiency [9]. It is confirmed that chemotherapeutic drugs lead to T-cell depletion, which is more serious in CD4+ than in CD8+ T lymphocytes, decline in dendritic cell function and an alteration in productivity of pro-inflammatory and anti-inflammatory cytokines.

Furthermore antineoplastic chemotherapy cause side effects like fatigue [10,11], skeletal muscle wasting and atrophy [12], also increased degree of tumor necrosis factor, inactivity and weight loss.

Improvement of immune function defend from side effects caused by chemotherapy. Immunotherapy agent boost populations of T-cells, dendritic and natural killer (NK) cells that are main powerful effectors in host antitumor response. Immunotherapy agents considered as alternative therapy and administered to enhance antitumor immunity and to improve clinical outcome to cancer chemotherapeutic treatment.

## Materials and Methods

Conceptual review was made of studies conducted on common autoimmune diseases and immune deficiencies such as cancers using IMPs. Searches included database of Ovid Medline, Science Direct, The Lancet, PubMed and Elsevier applying keywords of interested therapeutic area and IMPs.

## Results - Immunologic and Clinical Response

Positive responses to TF are confirmed through various tests: Delayed hypersensitivity skin test, reaction to alloantigen, mitogen: specific and non-specific types of T cell, NK cell activity, cytokines activity [2]. TF in osteosarcoma cases increased cell mediated cytotoxicity [13] and in Varicella cases with acute leukaemia in children and Herpes simplex virus improved T cell function [14-16]. Elevated C3 level restored to normal, no new infection, absence of eczema was observed in Wiskott - Aldrich syndrome [17]. Prostate cancer patients using TF during treatment showed higher survival rates among same group [18] and in HIV cases increased levels of Th cells and cytotoxic T cells [19]. Lung cancer patients using TF demonstrated longer survival rate [20]. TF in Hepatitis C cases stimulated Th1, which helps in viral particles clearing [21,22]. Administration directly to experimental glioma reduced tumor size and increased CD2+, CD4+, CD8+ and NK cell counts with increased apoptotic tumor cells percentage and tumor tissue expressing Th1 cytokines. Researchers observed additive antitumor effect of TF combined with chemotherapy [23].

Decrease of inflammatory infiltrates, morphological changes to similar of normal prostate, and prostatein decreased to basal levels was reported in DLE group with decreased CD45 expression and proinflammatory cytokines TNF-α, IFN-γ, IL-6, IL-17. In summary: DLE is able to modulate inflammatory response in experimental autoimmune prostatitis [24].

Prostate cancer is 2$^{nd}$ frequently diagnosed cancer in men worldwide. *In vivo*, DLEs reduced metastatic dissemination and inhibited tumour growth. DLEs antineoplastic effect correlated with changes in tumour infiltration, increased serum concentrations of IL-12 and CXCL1, reduced levels of vascular endothelial growth factor. Results: Antineoplastic impactassociated with immunomodulatory effect, not by direct effect on cancer cells, which indicate DLEs as beneficial adjuvant therapy in prostate cancer patients [25].

Breast cancer patients with DLE as adjuvant achieved metastatic lesions regression faster than control group. Subjects with metastatic breast cancer without DLE had persistent thyroid lesions and new lesion around aorta following 2 years of chemotherapy in contrast to group with retroperitoneal retrohepatic metastases with partial regression after 4 months of DLE treatment and 5 chemotherapy cycles [26]. TF as chemotherapy adjuvant associated with tumor regression and temporary cancer stabilization or reduced demand for other treatment modalities and have meaning as adjuvant therapy in certain malignancies [27].

Stage D3 prostate cancer survival rate on conventional therapy is very poor. During 1-9 years follow-up

complete remission obtained in 4%, partial remission in 12% and no metastasis progression in 28% patients. Median survival was 126 weeks, higher than survival rates reported in literature for same stage patients [18].

Osteosarcoma is malignant bone tumor with intention to metastasis and immune response loss of cytotoxic cells types. Assessment after surgery, neoadjuvant chemotherapy and specific TF showed that 63% patients increased T lymphocytes number, 75% increased cytotoxic T lymphocytes and 87.5% patients returned to phase I of Levins classification [28].

Disseminated renal cell carcinoma treated with TF as immune stimulant showed temporary metastases stabilization while patients without clinically evident metastases with high risk for recurrent disease remained disease free [29].

Nasopharyngeal carcinoma patient's refractory to conventional therapy treated with TF slowed tumor growth and associated with intense lymphocytic tumor infiltration and reconstitution of delayed cutaneous hypersensitivity reactions to microbial recall antigens which suggest favorable response to TF immunotherapy [30].

Myelosuppression is chemotherapy side effect along with lymphopenia, neutropenia and thrombocytopenia [9]. DLE protective effect demonstrated on NK cells together with CD4+ T, CD8+ T and CD19+ B lymphocytes. No myelosuppression in lymphoid populations observed in patients receiving DLE while without DLE absolute numbers of CD4+, CD8+ and B lymphocytes reduced. NK cells and B lymphocytes increased 1 month after chemotherapy with DLE as adjuvant. IL-3 levels dropped by 80% in control group without DLE compare to decrease by 34% only with DLE. IL-7 levels elevated with DLE by 11% decreased by 30% in control group [26].

The best outcome of neoplastic disease management are obtained by surgery in addition with chemotherapy and radiotherapy. All procedures influence immune system which often disturbed due to low leukocytes number, lymphocytes and side effects resulting from depressed immuninty. Immunostimulatory agents are helping to escape or minimize harmful effects like TF was used in cancer therapy by Fudenberg [31] and by other researchers in non neoplastic cases [31-33]. Regarding total leukocyte count, 65% patients presented 6-month increase in values and 83.3% in 12 months with leukocytes amount grow ranged from 1.9% to 103% and from 2.1% to 170% respectively. Total lymphocytes growth occured in 66.7% patients in 6 months and in 80% cases in 12 months. This elevation extended from 1.5% to 85% in 6 months and from 0.2% to 137.7% in 12 months. Statistical survey of these range was very significant [34].

Cancer and autoimmunity have general background, both attempt to supervise pulling immunity in opposite ways. Cancer and autoimmune diseases increase risks and treatments outcome and patients experience difficulty to stay in treatment protocol.

Autoimmune disorders cause inflammation which can lead to cancer. For example colitis or inflammatory bowel disease can rise chance of colorectal cancer. Chronic inflammation harm cell's DNA and may result in unlimited cell growth. In order to reduce inflammation immunosuppressors are frequently adviced and both assumed on increasing multiple cancers risk. Arthritis and psoriasis associated with increased lymphoma risk due to their pathophysiology, treatments or combination of these factors [35]. Autoimmune diseases treatment is complicated by risk of activating pathological process which possible to avoid with modern immunomodulatory therapy. With IPMs appearance there is hope for positive treatment outcome. Long-term therapy effect with IMP in 70% rheumatoid arthritis casesreported excellent, very good and good results. Among those 34.3% responded good, 37.1% showed very good outcome and continued treatment with nonsteroid products and IMP. 28.6% with stage 1 rheumathoid arthritis achieved excellent results and withdrawn nonsteroid therapy. Hence, TF adjuvant therapy may be considered benefitial for patients with rheumatoid arthritis [36].

Immunomodulation therapy may promise significant benefitsin management of dermatological autoimmune and inflammatory conditions [37,38]. Clinical data suggests that DLE in a form of STF may be used as a monotherapy or in combination with other immunotherapeutic modalities in management of eczema and other forms of dermatitis.

The 2 year, double blind, controlled TF trial in multiple sclerosis treatment showed drop on disability progression with remarkable outcome after 18 months from its commencement. Patients who received and continued TF demonstrated slower rate of multiple sclerosis progression compare to placebo group with significantly faster progression rate during trial, which slowed with TF treatment commencement. In addition, 470 patients with clinically definite multiple sclerosis are being treated in TF open study. Disease progression rate appears to be similar in patients who administered TF in initial trial. Follow-up study of 1980 TF trial patients and open study of 470 patients confirmed: TF has positive effect on slowing course of multiple sclerosis [39].

Although various mechanisms involving antibodies and different cell types take apart, Th1 and Th2 cells imbalance appears to perform one of main role in allergy formation. Another subpopulations: Th17, CD4 FOXP3 and Th9 positive regulatory T lymphocytes

also engaged in allergic response. TF induces mRNA expression of IFN-g, osteopontin, RANTES, and hBD-2 in human healthy subjects. TF was administered in different immune dysfunctions like allergies, immunodeficiencies, infectious diseases and tumors. TF recipients along with their conventional treatment frequently have better clinical evolution than without it, thus reach prompt and better resolution of allergic response [40].

## Discussion

IMP was well studied for more than half century. TF is potent to improve existing cell-mediated immunity responses also transfer information to identify and stimulate new response to various pathogens. Thereby it has been considered as essential tool, not only for treating, but also for preventing pathologies induced by them [31]. TF's pleiotropic properties shouldn't be overlooked, as lymphocyte extract comprises of fractions with both enhancer and suppressor features, carrying several antigenic specificities [5]. TF function in patients with virally induced cancers by increasing their potency to destroy respective virus and/or by increasing their capacity to recognize and eliminate novel formed cancer cells. Simultaneously, by stimulating suppressor cell functions, it promotes control of subsequent inflammatory processes [41].

Beneficial fact is that TF lack of viable cells which play role in graft versus host reaction, thus it is not immunogenic, contain no histocompatibility antigens. To specify target TF influence expression of antigen receptors on cells. Increased Th1 in turn repress production of Th2 and its cytokines like IL-4, IL-5, IL-6, and IL-13. TF promotes immune response mediated by cytokines that indirectly induce proliferation of hematopoietic progenitor cells in bone marrow [42]. DLE generally known as TF, is immunotherapy agent that demonstrated ability to improve immunological response in cancer patients [43,44]. The studies with DLE as adjuvant therapy have continually reported improvement in clinical response to treatment [45-47].

TF has important immune modulatory ability and lowers immunity to normal level in overreactions besides stimulates immune response, supports maturation and thymocytes differentiation, restores peripheral lymphocytesfunction, recovers humoral immunity via B lymphocytes differentiation, develops plasmocytes and synthesizes specific humoral antibodies, activates T lymphocytes and lymphokine production also increases activity of mononuclear phagocytic system [34]. Researchers confirmed that in control groups after several chemotherapy cycles quantity of lymphocytes decreased to below reference range. Contrary, in patients with DLE as adjuvant, CD4+ and CD8+ and B lymphocytes stayed within median value with increased NK cells amount after chemotherapy. It was concluded in many studies that DLE treatment supports considerably immunological recovery after numerous chemotherapy, ameliorate treatment compliance and quality of life during chemotherapy.

Therefore, TF gives attractive option to complement chemotherapy, which might strengthen immune system after disturbances following chemotherapy side effects [3,48,49]. Main TF benefit as immunotherapeutic agents is possibility to stimulate rapid immune reaction against pathogen within 24 hours and reducetime for patient immune response to 9-13 days [50]. Combination of results from different TF studies in one and extracting treatment outcomes of cancer with chemotherapy, autoimmune disorders, allergies also immunodefficiencies and infection diseases can be used by clinicians for decision-making and improving patient's life quality. Multiple studies showed TF as improving clinical and immunological response, symptomatology asabsolute lymphocytes numbers were always higher than expected as compared to control groups. TF doubtlessly accentuate immunological protection provided by DLE during chemotherapy. Median survival rates after metastases appearance is approximately 20-25 months and as time is limited it is higly important to obtain clinical response as fast as possible. It was observed that those metastatic patients receiving DLE demonstrated improved clinical responses within 6-12 months [26].

Cancer cases are more serious due to tumor itself in addition to chemotherapy or radiotherapy and corticosteroids, also affects immune system, contributing to immunosuppression accentuation. Different immunomodulators applied to reverse situation in purpose not only of improving immune response, minimizing chemotherapy side effects and radiotherapy, but of preventing protocols used to be interrupted, which compromises treatment results [51,52]. Lymphocytes with T subclasses are fundamental for immune reaction, particularly with respect to solid tumors. Thus, combats to this tumor type have objective of making T-lymphocytes active and competent [53,54]. It is obvious that TF stimulate leukocytes activation, total lymphocytes and their subclasses, leading to immune response induction [34].

TF can display multiple regulatory effects on individual aspects of immune system due to stimulation of expression of transcription factor retinoic acid receptor-related orphan receptor-gamma-t (RORγt) and enhances proportion of CD4+ RORγt+ cells, which in turn leads to stimulated expression of gene for IL-17 and increased IL-17production. As such main effect confirmed in pathway of Th17 cell development and IL-17 production [55]. IL-17 is highly pleiotropic cytokine having multiple effects in various immuno-

logical situations, including inflammation, autoimmunity, transplantation reactions, asthma and anti-tumour immunity [56,57], enhance local inflammatory reactions and modulate immune system functions [58,59]. This pathway may represent main mechanism of immunomodulatory and immunotherapeutic TF actions described in various models [60]. According to last half century studies DLE or TF determines wide range of possibilities to use but due to TF is complex group of many low molecular weight proteins (more than 200), its precise molecular structure and mechanisms of action have not been elucidated yet, which means different studies might be using different TFs and as such need more comparable research conducted. However its use in clinical practice as IMP is absolutely valuable but before administration it is important to evaluate specificity, potency, and best dose, trying to individualize treatment for each patient [61].

At present time, prediction and prevention positioned as pillars of medicine. TF is prospective candidate for prevention and treatment of existing and novel emerging pathogens including their clinical appearance. Inflammation, contrariwise, must also be managed by suppressing infections and also by direct impact on its complex mechanisms by inducing power of suppressor lymphocytes and controlling cytokine secretion. TF's significant advantages are: efficiency on treating and preventing infections, reasonable manufacturing price, safety and absence of toxicity. Indeed, TF are universal immunocorrectors with proven multiple studies effects.

## Conflict of Interest

There are no conflicts of interest to declare.

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