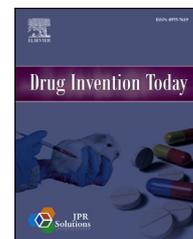


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## Review Article

# A review on transfer factor an immune modulator



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### ABSTRACT

**Aim:** To understand what is transfer factor and its significance in stimulating immune system which is necessary for the general maintenance of health.

**Methods:** Articles were collected from net sources.

**Results:** Basics, mechanism of action, safety aspects of transfer factor were discussed in this review. Diseases showing positive result with transfer factor treatment are tabulated.

**Conclusion:** From this it is concluded that it is a dialyzable, active protein initiator molecule able to transfer cell mediated immunity from healthy donor to recipient who is non-immune thus keeping one away from infection.

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## 1. Introduction

Transfer factor is a natural, non-species specific, tiny, small peptides of 3500–6000 kDa in molecular weight, transparent, light yellow fluid having pH 6.5–7.0, composed of oligoribonucleotides attached to a peptide molecule that are inherent in all animal bodies, said to be non-allergic because of their small size and act as immunomodulator, RNA might provide a cytophilic property. Dr. Kirkpatrick<sup>1</sup> identified highly conserved region of amino acids in transfer factor that are able to bind to the target cells with high affinity. Higher tyrosine, glycine content are present in some variants. The first milk in all mammalian mother called colostrums, a god's gift which gives passive immunity to newborn babies, has been proven to contain transfer factor, non-antigen specific moieties present in colostrum might contribute for the beneficial outcome in patients by stimulating their immune system non-specifically and are universally effective. H. Sherwood Lawrence demonstrated this passive transfer of immunity in 1949.<sup>2,3</sup> It can also be obtained from immune donor

lymphocyte who is able to transfer cell mediated immunity to a non-immune recipient. This helps to act against bacterial, viral, parasitic infection, autoimmune diseases, diabetes, autism, infertility, psoriasis, retinitis pigmentosa, asthma, cancer.<sup>4–6</sup> The positive responses are confirmed through various tests such as delayed hypersensitivity test on skin, response to alloantigen, specific and non-specific mitogen, type of T cell, NK cell activity, cytokines activity. Since, transfer factors are acquired in our bodies through natural immune system and able to perform catalytic function in immune system triggering effect without getting consumed,<sup>4</sup> this review aimed to provide briefly its mechanism of action once synthesized, immunological role in aiding cell mediated immunity as it is having extraordinary benefits.

## 2. Sources

Birds have transfer factor inside their eggs providing a library of immune system and identifiers to make out the attacking

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pathogen.<sup>7</sup> Transfer factors are synthesized from animal, human sources by injecting with certain pathogen to produce specific transfer factor. Transfer factor generated using human blood are human derived, cow and mouse spleen are bovine, murine derived. Viza and his coworkers in 1974 observed that transfer factor with known antigenic specificities can be generated from LDV/7 lymphoblastoid cell line.<sup>8</sup> The dialyzable transfer factors have onset period as hours and able to maintain its effectiveness for five years. Transfer factor can be purified by high performance liquid chromatography and column chromatography.

### 3. Mechanism of action

Transfer factor lack viable cells that play a role in graft versus host reaction, not immunogenic, contain no histocompatibility antigens.<sup>9,10</sup> Natural immune response is a causative factor for the production of transfer factor and they are produced within T helper cells (Fig. 1), once released, the immune system activity is influenced in several ways and studied by other cells involved in immune system which indicates, that T helper cells are active in fighting against the pathogen, thereby stimulating the production of new helper T cells, Natural killer cells, macrophages, cytotoxic T cells. Thus, marching close to the target most probably by influencing the expression of antigen receptors on cells. Increased Th1 in turn repress the production of Th2 and its cytokines like IL-4, IL-5, IL-6, and IL-13. A remarkable feature of transfer factor is eliciting multiple, opposing function<sup>11,12</sup> or bio feedback mechanism by antigen specific, inducer, suppressor/regulatory fraction contained in it. Here, antigen specific fractions aid the function of recognizing and memorizing pathogenic organisms in a more faster manner. Secondly, inducer fraction increases the antigenic stimulus whereas, suppressor fraction act by releasing IL-10, an inhibitory cytokine from Th2 cells, playing a vital role in controlling immune over reactions, mistargeted reactions in the development of autoimmune disorders. Kirkpatrick demonstrated that *in vivo* administration of transfer factors to mice, afford the recipients spleen cells with the property of responding to target antigen *in vitro*

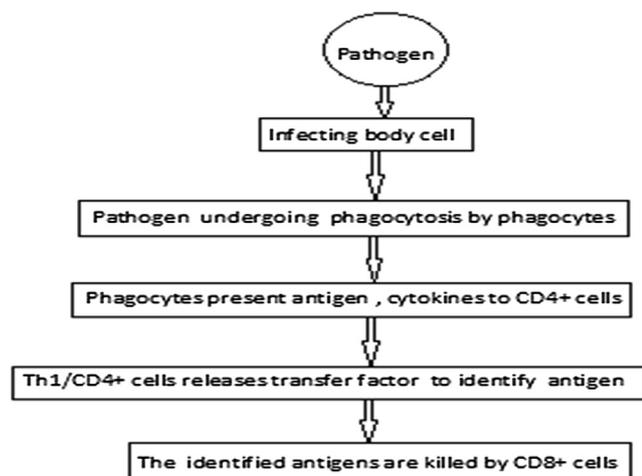


Fig. 1 – Showing synthesis of transfer factor.

by secreting gamma interferon,<sup>13</sup> a product of Th1 cells, IL-2, TNF-alpha thereby ensuring the development of cell mediated immunity. While stimulating cell mediated immunity, it does not increase antibody secretion as well its responses against the same specific antigen. So, transfer factors develop cell mediated responses in patients who are suffering from immunodeficient, infectious disease, as well as in disorder with certain anergies. Maturation of naive T cells as well as increased cell mediated immunity are regulated by thymic factors. It is agreed that transfer factor is more effectual in educating naive cells about the approaching danger. So, in the treatment of mild thymic primary immunodeficiency, both thymic and transfer factors are suggested.<sup>14,15</sup> Several factors that decrease cell mediated immunity, Th2 supremacy are age, cytotoxic cancer treatments, stress developed after surgery, metastatic diseases.<sup>16</sup> Thus, cell mediated immunity plays a major role in judging the morbidity and mortality above sixty years.

### 4. Transfer factor and diseases

The immune system is a versatile system encompasses more than a trillion cells, weighing about 1 kg and helps in recognizing, fighting, remembering invading pathogens. Each pathogen can bring out transfer factor, atleast one transfer factor is created for every piece of pathogen that the immune system faces. Transfer factors influence the activities of various immune components and also regulate cytokines.<sup>17</sup> Imbalances in the production of transfer factor lead to the development of rheumatoid arthritis, cancer, Alzheimer's, heart disease, hepatitis and so on. The time taken for complete development of immature immune response/delayed hypersensitivity is 10–14 days, but transfer factor induces an immune response in within 24 h.<sup>18</sup> IMREG I and IMREG II<sup>19</sup> help in bringing out balanced immune system. Fudenberg's, three important measures that have to be taken care are antigenic specificity, strength of the extract and recipients immune status<sup>20</sup> and also the right dose. Vetto et al reported that patients in advanced cancer stages were not able to respond when they were treated with antigen induced lymphocyte transformation.<sup>21</sup> Few diseases that were studied with transfer factor are depicted in Table 1.

### 5. Stability and safety of transfer factor

Transfer factor can resist freezing, withstand treatment with DNase, pancreatic RNase, and trypsin<sup>34</sup> but destroyed by snake venom phosphodiesterase. No bad side effects have been reported so far with transfer factor,<sup>35</sup> and valuable when administered orally as well as by injection.<sup>17,36</sup> Long-term oral administration is convenient,<sup>37</sup> safe<sup>38,39</sup> and easily accepted<sup>37</sup> by infants, elderly people who are at the risk for numerous infections. Dresseler and Rosenfield<sup>40</sup> reported, that heat lability of transfer factor depends on the melting of a double stranded nucleic acid, full activity was retained at 80 °C, above 90 °C destroyed the activity, had an intermediate activity at 85 °C but stable to cold and consequently, able to retain its biological activity even after storing at –20 °C to –70 °C for

**Table 1 – Showing few diseases studied with transfer factor.**

Diseases showing positive result on treatment with transfer factor	Effects	References
Osteosarcoma	Increased cell mediated cytotoxicity	Fudenberg 1976 <sup>22</sup>
Varicella with acute leukaemia in children		Steele et al, 1980 <sup>23</sup>
Herpes simplex virus	Improved T cell function	Steele et al, 1976 <sup>24</sup>
		Viza et al, 1986 <sup>25</sup>
Wiskott–Aldrich syndrome	Increased C3 level returned to normal, no new infection, absence of eczema	Levin et al, 1970 <sup>26</sup>
Glioma	Reduces the tumour size, and increases CD2+, CD4+, CD8+ and NK cell counts, apoptotic tumour cells	Pineda et al, 2005 <sup>27</sup>
Prostate cancer	Higher survival rates	Pizza et al, 1996 <sup>28</sup>
HIV	Increased levels of helper T cells and cytotoxic T cells	Granitov et al, 2002 <sup>29</sup>
Lung cancer	Longer survival	Pilotti et al, 1996 <sup>30</sup>
Hepatitis C	Stimulates Th1, which helps in clearing of viral particles	31,32
Chronic mucocutaneous candidiasis	Restored cellular immunity	33

several years. Since, transfer factors are derived from blood products it will be safe to check for HIV/AIDS/hepatitis to get rid of blood borne diseases.

## 6. Conclusion

The life we are living must be healthy as long as we are. Everyone is aware, that our immune system gets activated only when we are exposed to infection. Hence, greater the exposure, better the immunity. To conclude, transfer factor is an immune enhancing molecule produced naturally by our immune system aiding immunological memory of recipient. It is not a drug or vitamin to cure our illness but it acts as a channel to our immune system. So, a balanced immune system is attained. Eventhough, they found to be useful, the success rate varies depending upon the preparation of transfer factor, the right dose selected, the potency, the degree of illness and duration of infection.

## Conflicts of interest

The author has none to declare.

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## REFERENCES

- Kirkpatrick Charles H. Transfer factors: identification of conserved sequences in transfer factor molecules. *Mol Med.* 2000;6:332–341.
- Lawrence HS. *Transfer Factor in Cellular Immunity*. In: *Harvey Lecture Series*. vol. 68. New York: Academic Press; 1974:239–350.
- Lawrence HS. The transfer in humans of delayed sensitivity to Streptococcal M substance and tuberculin with disrupted leukocytes. *J Clin Invest.* 1955;34:219–232.
- Fudenberg HH, Pizza C. Transfer factor 1993: new frontiers. *Prog Drug Res.* 1994;42:309–400.
- Pizza C, DeVinci C, Fudenberg HH. Transfer factor in malignancy. *Prog Drug Res.* 1994;42:401–421.
- Transfer factor in the era of AIDS: the proceedings of the Xth international symposium on transfer, 22–24 June 1995, Blonga, Italy. *Biotherapy.* 1996;9:1–185.
- Hennen WJ, Lisonbee DT. Methods for obtaining transfer factor from avian source, composition including avian generated transfer factor and methods of use. United States patent 6,468,534; Oct 22, 2002.
- Viza D, Boucheix C, Cesarini JP, et al. Characterization of a human lymphoblastoid cell line, LDV/7, used to replicate transfer factor and immune RNA. *Bio Cell.* 1982;46:1–10.
- Lawrence HS, Landy M, eds. *Mediators of Cellular Immunity*. New York: Academic Press; 1969.
- Lawrence HS. Transfer factor. *Advan Immunol.* 1969;11:196–261.
- Alvarez Thull L, Kirkpatrick CH. Profiles of cytokine production in recipients of transfer factor. *Biotherapy.* 1996;9:55–59.
- Borkowsky W, Lawrence HS. Antigen-specific inducer factor in human leukocyte dialysis: a product of T helper cells which bind to an anti-V region and anti-Ia region antibodies. In: Kirkpatrick CH, Burger DR, Lawrence HS, eds. *Immunobiology of Transfer Factor*. New York: Academic Press; 1983:75–89.
- Kirkpatrick CH, Chandler JW, Schimke RN. Chronic mucocutaneous moniliasis with impaired delayed hypersensitivity. *Clin Exp Immunol.* 1970;6:375–385.
- Lawrence HS. *Immune Regulation in Transfer Factor*. New York: Academic Press; 1979:613.
- Khan A, Sellars WA, Gabela P, Thometz D. Transfer factor, thymosin and E rosettes. *NEJM.* 1975;292:868.
- Nicolini A, Ferrari P, Spinelli R, Carpi A, Sagripanti A, Amborgi F. Cell-mediated immunity in breast cancer patients. *Biomed Pharmacother.* 1996;50:337–343.
- Kirkpatrick CH. Activity and characteristics of transfer factors. *Biotherapy.* 1996;9:13–16.
- Lawrence HS, Borkowsky W. Transfer factor current status and future prospects. *Biotherapy.* 1996;9:1–5.
- Sizemore RC, Dienglewicz RL, Pecunia E, Gottlieb AA. Modulation of concanavalin A induced, antigen-non-specific regulatory cell activity by leuencephalin and related peptides. *Clin Immunol Immunopathol.* 1991;60:310–318.
- Fudenberg HH, Fudenberg HH. Transfer factor: past, present and future. *Annu Rev Pharmacol Toxicol.* 1989;29:475–516.

21. Vetto RM, Burger DR, Lilley DP. Proceedings: evaluation of immune status in tumor patients. *Arch Surg.* 1974;108:558–560.
22. Fudenberg HH. Dialyzable transfer factor in treatment of human osteosarcoma: an analytic review. *Ann N Y Acad Sci.* 1976;277:545–557.
23. Steele Russell W, Myers Martin G, Vincent Monroe M. Transfer factor for the prevention of *Varicella zoster* in childhood leukemia. *N Eng J Med.* 1980;303:355–359.
24. Steele RW, Heberling RL, Eichberg JW, Eller JJ, Kalter SS, Kinker WT. Prevention of Herpes simplex virus Type 1 fatal dissemination in primates with human transfer factor. In: Ascher MS, Gottlieb AA, Kirkpatrick CH, eds. *Transfer Factor: Basic Properties and Clinical Applications.* New York: Academic Press; 1976:381–386.
25. Viza D, Vich JM, Phillips J, Rosenfeld F, Davies DA. Specific transfer factor protects mice against lethal challenge with Herpes simplex virus. *Cell Immunol.* 1986;100:555–562.
26. Levin AS, Spittle LE, Stites DP, Fudenberg HH. Wiskott–Aldrich syndrome, a genetically determined cellular immunologic deficiency: clinical and laboratory responses to therapy with transfer factor. *Proc Natl Acad Sci U S A.* 1970;67:821–828.
27. Pineda B, Estrada Parra S, Pedraza Medina B, Rodriguez Ropon A, Pérez R, Arrieta O. Interstitial transfer factor as adjuvant immunotherapy for experimental glioma. *J Exp Clin Cancer Res.* 2005;24:575–583.
28. Pizza G, De VC, Cuzzocrea D, et al. A preliminary report on the use of transfer factor for treating stage D3 hormone unresponsive metastatic prostate cancer. *Biotherapy.* 1996;9:123–132.
29. Granitov VM, Karbysheva NV, Sultanov LV, McCausland CW, Oganova EA. Use of activated transfer factor in treatment of HIV-infected patients. *Russ J HIV/AIDS Relat Probl.* 2002;6:79–80.
30. Pilotti V, Mastroianni M, Pizza G, et al. Transfer factor as an adjuvant to non-small cell lung cancer therapy. *Biotherapy.* 1996;9:117–121.
31. Milich DR, Chen MK, Hughes JL, Jones JE. The secreted hepatitis core antigen can modulate the immune response to the nucleocapsid: a mechanism for persistence. *J Immunol.* 1998;160:2013–2021.
32. Tsai SL, Liaw TF, Chen MH, Huang LY, Kuo GC. Detection of type-2 like T helper cells in hepatitis C detection: implications for hepatitis C virus chronicity. *Hepatology.* 1997;25:449–458.
33. Masi M, De Vinci C, Baricordi OR. Transfer factor in chronic mucocutaneous candidiasis. *Biotherapy.* 1996;9:97–103.
34. Lawrence HS. Lawrence HS, ed. *Cellular and Humoral Aspects of the Hypertensive States.* New York: Harper; 1959:279–319.
35. Khan A, Sellars W, Grater W, et al. The usefulness of transfer factor in asthma associated with frequent infections. *Ann Allergy.* 1978;40:229–232.
36. Kirkpatrick CH, Hamad AR, Morton LC. Murine transfer factors: dose–response relationships and routes of administration. *Cell Immunol.* 1995;164:203–206.
37. Wu S, Zhong X. Observation of the effect of PSTF oral liquor on the positive tuberculin test reaction. *Chung Kuo I Hsueh Ko Hsueh Yuan Hsueh Pao.* 1992;14:314–316.
38. Pizza G, De Vinci C, Fornarola V, Palareti A, Baricordi O, Viza D. In vitro studies during long term oral administration of specific transfer factor. *Biotherapy.* 1996;9:175–185.
39. Jones JF, Jeter WS, Hicks MJ. Oral transfer factor use in the hyper IgE syndrome. In: *Immunobiology of Transfer Factor.* New York: Academic Press; 1983:61–70.
40. Dressler David, Rosenfield Steven. On the chemical nature of transfer factor. *Proc Nat Acad Sci USA.* 1974;71:4429–4434.