Scientific Evidence Documents the Immune Functions of Transfer Factors: Education, Enhancement and Modulation.

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The successful application of transfer factors (TF) for immune wellness depends upon the understanding of its biological functions in nature and as a dietary supplement. Needed is a consensus among TF experts and those using TF about the roles of TF in human and animal wellness.

It is the purpose of this review to move the conversation about TF toward this consensus. The literature on TF is broad in scope, international and spans over 60 years of research reported in scientific journals, proceedings and texts. This review employed the literature database at 4Life Research LLC and that of the National Institutes of Health via the *Pub Med* database. The databases were queried using synonyms for the three general functions of transfer factor to extract those publications that describe antigen specificity, non-specific immune enhancement or immune regulation (Table 1). The numerous reports were examined for results and opinions based on controlled research data. Those papers selected for this review were chosen for their scientific merit and the demonstration of significant description of data supporting properties that have biological implications for immune physiology and immune wellness. Only a few clinical reports are cited due to small sample size or inadequate control observations, yet suggesting immune functions for this important group of unique peptides.

Note : The references are organized in three groups. The citations showing the name and year are citations from the 4 Life database. Citations with a number are additional references supporting the data discussed. Lastly a bibliography from Medline Pub Med for TF publications provides addition background.

Education Function:

Transfer Factor is the informational molecule that provides for specificity of antigen recognition and hence immune memory. For the sake of brevity and ease of communication this attribute shall be called the Education Function. Over the span of six decades research has evolved from the early clinical observations in human subjects to very precise molecular research. The data are very conclusive. TF is the means by which the immune system recognizes potential threats and then stores that information on the surface of long lived T Cell Lymphocytes as an integral part of the T cell receptor.

The transfer of immune information from donors with immune information to immunologically "naïve" recipients was first described contrary to popular notions by Chase (1945). In this work, whole leukocytes from sensitized guinea pigs were transferred to un-sensitized guinea pigs and in so doing conferred Delayed Type

Hypersensitivity (DTH) skin responses in the naïve animals. DTH is a manifestation of cellular recognition and localization to the site of antigen. DTH occurs over a period of 24 to 72 hours and is confirmed by histology revealing a local mass of mononuclear cells. This reaction is that of the Purified Protein Derivative (PPD) used clinically today for screening and detecting persons immune reactive to TB.

Chase's work likely inspired Lawrence in 1949 to extract small molecules from leukocytes from humans sensitized and skin reactive to tuberculin. The dialysate of these ruptured leukocytes is called DLE or dialyzable leukocyte extract. It is the DLE that transferred the information that made tuberculin non-reactive subjects reactive and in a very short time after receiving the DLE from tuberculin reactive subjects. Later Lawrence (1955) showed that similar "transfers" of immune information could be conducted with microbial substances from streptococci. Lawrence (1957) went on to demonstrate antigenic exposure created specificity in DTH reactions and that could be induced in donors by exposure to unique antigen and only present in the DLE after exposure. Moreover, he was able to serially transfer immune memory via DLE from one donor to a recipient, establishing that the information in DLE is replicated in sufficient cells so as to be transferred to persons well removed from the original DLE administration. Thus it is appropriate that Lawrence be credited with coining the term "transfer factor" after his definitive work.

This *in vivo* work in the limited numbers of human subjects had its detractors citing the uncontrolled variables in the human pathogen exposure history and immune physiology. Hence when Valentine and Lawrence (1969) ran immune information transfer experiments, but this time *in vitr*o some of the criticisms were addressed. They demonstrated that a soluble factor from sensitized white blood cells could transform naïve cells into PPD responsive as measured by cell proliferation *in vitro* by measuring DNA synthesis in cloning cells. This demonstrates clearly that "educated" lymphocytes will proliferate in the presence of the antigen to which they are programmed. Ascher (1974) went on to repeat this work in a more refined and reproducible *in vitro* assay and demonstrated specific cell proliferation effects of antigen on TF educated cells. They also showed that this was not a non-specific adjuvant effect. An adjuvant effect would cause the proliferation of all lymphocytes regardless of TF informational priming.

Salaman (1975) took the work a step further and documented that TF-DLE was not species specific. The work showed that human DLE from PPD reactors could sensitize guinea pig lymphocytes that in turn when exposed to tuberculin would show evidence of recognition in the leukocyte migration inhibition (LMI) test. LMI is a correlate of cellular immune responsiveness measured by cutaneous DTH. LMI is the effect of cytokines secreted from stimulated T Cells that retard migration of mononuclear cells away from a well in agar media when they are educated and exposed to the recognizable antigen. *In vivo* this effect is said to be chemotactic and a cellular immune response draws and hold mononuclear cells to the site of infection or antigenic challenge. Today we know these functions arise as a result of programmed cytokine secretion by activated T cells.

The work by Bell (1976) and others (Burger 1976, and Cohen 1976) showed very clearly that naïve lymphocytes must be "educated" by TF-DLE before they would proliferate in response to antigen. This is the first inference that TF "educates" the immune system and that concept has persisted to date.

The clonal expansion of educated lymphocytes is a critical step for infection control. The rapid increase in specific T cell clones in necessary for prompt pathogen reduction. The data further suggests that the TF in DLE was the recognition factor for the antigenic "educational" commitment of the T lymphocyte necessary for antigen recognition and the all-critical clonal expansion. The immune system highly regulates the clonal expansion process, such that is does not occur without ample immune justification. This control is critical to avoid gross immune response inefficiency and autoimmunity.

The properties of human DLE were further refined by Lawton (1977) were in they used ultra filtration and gel chromatography to further isolate and concentrate the active components of DLE. The concentration of the factor provided for more vigorous DTH responses when the sensitized recipients' were tested with antigen. This suggests that the educational role of TF is somewhat dose dependent, although they did not do a formal dose titration experiment. It may well be that the dose of the TF information influences the number of educated and responsive T cells and thus the magnitude of the response.

In mice, the experiments by Rifkind (1977) demonstrated that DLE sensitization occurring within 24 hours to three different types of microbial antigens. There was no evidence of a non-specific adjuvant effect. Other researchers confounded the interpretation of the research to date when they described a non-specific cell proliferation response. This led some to conclude that TF from DLE was not antigen specific. Wilson and Fudenberg (1979) fractionated DLE and were able to sort out some of the confusion. They showed that yes indeed there was both specific and non-specific fractions and effects as measured through the LMI test.

The suggestion the TF in DLE might be non species specific was addressed by Schindler (1979) and Klesius (1979) Here they showed that human and bovine DLE could sensitize mice and do so to novel antigens that mice could not be exposed to naturally. This work thus strongly suggests TF from DLE is active across species and inducible to novel antigens. It refutes the notion that antigenic recognition is specifically orchestrated by encoding in the genetic information. This further supports the premise of strict antigenic specificity for TF and cell recognition.

To further elucidate the mechanism of immune information transfer of TF DLE it is useful to find a way to precisely block the transfer of antigenic recognition information. Borkowsky and Lawrence (1980) succeeded. When a specific antigen was linked with polystyrene and it would still bind to the transfer factor. The combination however blocked the sensitization of naïve lymphocytes. When tested the animals showed negative LMI tests whereas the positive uncoated controls gave positive LMI test showing evidence of antigenic education. If there were other

mechanisms for antigen information transfer, the blockage experiments would have failed or otherwise given equivocal results.

As immunology entered the era of molecular biology, Kirkpatrick's group (1986) performed as series of elegant experiments with mice TF DLE to the novel antigens ferritin and cytochrome C from other species. They were able to induce cell-mediated immunity to these antigens as measured in the footpad assay. The footpad assay is a proportional swelling reaction to injected antigens like that of DTH. Moreover they were able to show that antigen binds specifically to the transfer factor produced to it by lymphocytes. It binds much like antibody binds to its antigen and antibody chemistry provides a good correlate to understanding TF specificity. To confirm the specificity of the passively acquired T Cell immunity Kirkpatrick (1986) synthesized novel poly-amino acids and demonstrated DTH is mice administered the specific DLE. There was no cross reactivity with other slightly dissimilar peptides thus confirming the molecular specificity of TF.

The Kirkpatrick group went on to conduct the definitive research on the molecular nature of TF from DLE. They demonstrated that binding it to its corresponding antigen on a column and then eluting the TF from the column could purify a unique antigen type of TF. Thus the TF obtained in quantity was for only one type of antigen and confirming this in a series of DTH footpad assays (1994). Then Kirkpatrick (2000) revealed that any TF molecule has a constant region of about 10 amino acids and that this is the region that binds to the T cell receptor. He showed this by synthesizing the peptide and and then demonstrated that naïve T cells were blocked from receiving TF docking and no DTH could be observed. He went on to suggest that 20 to 30 amino acids make up for the variable region on TF and this region codes for the specificity and provides for the 3 dimensional recognition of antigen.

Currently molecular immunologists are intensely researching this interaction at the complex T cell receptor. The specific recognition of antigen at the T cell receptor is aptly described as "docking (7). To "dock" is to match the conformations of the recognition peptide (TF) with the antigen in a lock and key type interaction. The T cell receptor and interaction occurs as what is called the "immune synapse" and this process can be visualized experimentally and reveals many other cofactors that are also involved at the synapse (8).

From all of this research a model emerges of TF specificity that is analogous to the "foot print in the sand". Feet and TF have similarities that may allow for some cross reactivity yet specific enough to prevent misidentification that could precede autoimmune reactions. The information in the sand imprint is a natural process that can be manipulated. It can be transferred naturally as well as exogenously.

At this time, from decades of research, we can confidently infer that TF is the immune memory molecule and the informational determinant of the adaptive immune system. It provides for the specific immune recognition and resistance provided by exposure, vaccination and maternal transfer via cord blood or colostrum.

Testing the ability of TF to modulate disease is a logical question for researchers. Can TF administered exogenously alter the infection and the outcome of a disease? Perhaps the real test of TF specificity and ability to fore arm the immune system come from challenge infection models with pathogens of known potential for morbidity and mortality. It is one thing to show a specific DTH or immune cell proliferation and yet it may be insufficient or unable to protect the animal from potentially lethal challenge.

Addressing this question Smith (1983) protected naïve mice from lethal salmonella infection with a murine derived TF DLE (1). Fayer (1989) was able to confer immunity in neonatal calves from potentially lethal diarrhea from the parasite cryptosporidium, by the administration of a bovine derived TF. Crytosporidia infect the intestinal epithelium and have an intracellular cycle of infection. Effective T cell immunity is necessary for the protection and resolution of the severe diarrhea it causes. In humans with advanced HIV infections this parasite and the infection it causes may be a major cause of mal-absorption of nutrient in AIDS patients. Using bovine colostral TF, Borkowsky (1989) orally administered TF to such patients. It achieved control of diarrhea and stool pathogen elimination in most patients in this small trial. It did suggest however that orally administered colostral TF was efficacious in some patients.

Pizza (1986) created a bovine TF to Herpes Simplex One (HSV1). This virus has a high lethality for mice. Similar challenge studies with mouse specific mouse derived TF and HSV 1 provide corroborating data (Huang 1987). Pizza (1999) went on to demonstrate that orally administered specific TF significantly reduced the clinical recrudescence of human oral and genital herpes.

Perhaps one of the more definitive works and the basis for a USDA vaccine license is that of Schuler and Wilson (1989). Cows were vaccinated with the swine transmissible gastroenteritis (TGE) virus. Colostrum from these cows was harvested and processed by ultra filtration to exclude molecules greater the 10 KD. The ultra filtrate was fed to neonatal pigs and subsequently challenged with a potentially lethal dose of the virulent TGE virus. Animals that received the TGE colostral TF had a 70% reduction of mortality over controls. This work demonstrated the necessary efficacy data to obtain a vaccine license. More importantly it reveals that cow colostrum is a source of TF that (1) can be readily processed for its TF content, (2) that the TF can be induced by exposing the cow to antigen (TGE), (3) the colostral TF is absorbed and effective orally beyond 48 hours in neonates, and (4) the TF can confer a protective immune response.

Given this work with a variety of species, sources of TF and different disease agents it is clear the educational function of TF can provide for significant immune protection from infectious disease and is the direct consequence of immune recognition provided by exogenous TF.

The work with Bovine colostrum documenting it as a source of TF does raise some questions about how it may or may not be similar to DLE, since DLE is the substrate that most research reported here and elsewhere is predicated.

The question about how the mammary gland protects itself and its role in protecting the health of the neonate was the focus of some research that addresses the question about colostral TF and that of DLE. In 1977 Bennett (2) examined the secretions of the bovine mammary gland days prior to parturition. They showed the secretion contained myriads (>50K/ml) of small mononuclear cells that were subsequently shown to be T Cells of the CD4+ and CD8+ types (6,14). The cells were mostly viable yet large percentages were in the stages of cell death or apoptosis. At the time of parturition the volume of secretion greatly increases and has the characteristics of whole colostrum. Ultra filtrates of this colostrum are shown to provide TF immune attributes like those of DLE.

The ungulate (cloven hoofed animals) placenta is four layers thick. Unlike primates and some other species small and large peptides do not cross the placental barrier, thus colostrum is the only source of both passive (antibody) and active (TF) immune protection for the neonate. It is well established that colostrum deprived ungulate neonates perish soon after birth from pathogens known to be controlled by specific antibody or specific cellular immunity in their colostrum fed counter parts (9,13).

From the forgoing and in the absence of controlled research suggesting otherwise, it is clear that the small peptide called transfer factor is created by immune cells for the purpose of generating information that becomes immune memory. This immune memory is similar if not identical in all higher animals, is active across species lines, is active orally and is pivotal for the protection and resolution of infection. Transfer Factor is the immune memory molecule with the primary purpose to educate the naïve T Cell and create a lasting cellular immune memory.

Enhancement Function:

The available evidence suggests that TF from any source has abilities to enhance or otherwise support immune functions and the mechanism appears to be separate but related to its educational functions. Just the same, the immune enhancing effects appear to be quite significant yet confounding. The less than additive or linear mechanistic observations of this effect may be due to the conditional or situational signaling that occurs in the highly regulated immune control systems. Thus the distinction between the enhancing and balancing effects of TF may well overlap significantly.

Gallin (1974) reports that TF DLE subfraction had chemotactic abilities for neutrophils and to a lesser extent monocytes when injected into the skin of rhesus monkeys. The sub fraction of the DLE was 5KD or less in size. This finding suggests that TF DLE in and of itself does not contain cytokine substances that would attract and hold monocytes. Most of the cytokines and interleukins are much larger in size. This affect as observed in other studies, occurs when TF primed and antigen stimulated T cells generate a positive LMI response from cytokines secreted by the activated lymphocytes.

An insight into the molecular role of TF DLE came from the work of Sandler (1975) where they examined the effect of TF on the intracellular signaling molecule, cyclic

nucleotide (cGMP). TF DLE increases cGMP in monocytes and it has a role in allowing the expression of immune functions of these cells. They did not differentiate which mononuclear cells hence this may apply to the NK cell as well and an early identification of how TF improves NK function. Similarly, a nonspecific fraction of TF DLE was able to augment skin DTH to novel and PPD injections. This augmentation was mild and did not confer reactivity in non-sensitized persons, thus suggesting it is different from the antigen specific components of TF DLE (Krohn 1976). Archer (1976) further elucidated this phenomenon *in vitro* demonstrating a fraction of TF DLE that non-specifically enhances lymphocyte proliferation to antigen. Littman (1977) confirmed this work using the lymphocyte blastogenesis response to antigen and sub fractions of TF DLE. Wilson (1979) provides similar results looking a factions and their effect on the LMI assay and demonstrate antigen dependent and independent fractions.

The regulatory interleukins play a pivotal role in immune responses. Alvarez-Thull (1996) working in Kirkpatrick's lab, reports that mice exposed to HSV had spleen cells that elaborated IL-2 and INF gamma and little or no IL4 or IL10 in response to TF DLE. In particular IL2 is a potent up regulator of THI activity and a down regulator of TH2 responses, whereas IL4 and 10 have the opposing effect.

The NK or Natural Killer T Cell does not use or require antigenic recognition to peruse its functions, yet there is strong evidence that TF or some fraction thereof has potent NK cell activity. Hamprecht (1989) reports that an acid DLE fraction specifically stimulated mononcytes shown to be CD16 or NK cells. The activity of these cells in the K562 NK cell assay was markedly enhanced by the DLE fraction. Remarkably similar work by Doelker (1989) also demonstrated activity of monocytes against tumor cells. These monocytes were CD3- and CD8- and CD16+ and thus NK cells. Some of the NK cells also have a CD8+ receptor. This basic fraction differs slightly form the acid fraction described by Hamprecht yet have similar biological function and most likely interact with different NK cell receptors. This fraction was 1 KD in size.

Bovine and avian derived transfer factors were evaluated in an *in vitro* NK cell assays using pooled mononuclear cells from healthy adults. TF from a single species and when combined in various ratios yielded an 80 to 98% increase in the NK cell destruction of the K562 target cancer cells. This result was greater than that for IL-2 at 88%, thus TF may effect the elaboration of the other cytokines like IFN gamma (10). Similar results were obtained in a variant NK assay with sub fractions of TF 2.5 KD or less, thus this enhancing fraction is likely distinct from transfer factor per se that has a molecular size of approximately 7 KD (Kirkpatrick 2000).

The first report of TF improving the humoral or antibody responses was in rabbits. Here TF DLE quite substantially increased the antibody titers to unique antigens in vaccinations. Roda (1978) further suggests that the TF may be acting on the T Helper Cell that facilitates enhanced antibody production via the shift from IgM to high titers of IgG. Salaman (1979) notes in a brief report that TF DLE was given with

sheep RBC's it produced a distinct rise in anti-RBC titers over controls. Hence for some time we have had early reports of antibody enhancement, yet the mechanism appears to be circumspect through the TH2 cell system.

The first and only report of the effect of TF on the S-IgA antibody system originated from the R and D labs of 4life Research (3). The work demonstrated that TF given orally significantly influenced Salivary SIgA. Healthy adults given TF containing products increased the salivary SIgA in 100% of the subjects by 73%. There was a trend that suggested the biggest increases in SIgA production occurred in those with lower baseline levels although it was not a prerequisite.

There are many reports of the clinical use of TF in persons with immune compromise and opportunistic infections. Most of these are persons with diseases that compromise, like HIV, and those with inherited conditions. These reports while quite interesting do not shed any mechanistic information about the actions of TF, apart from some evidence of temporary immune reconstitution.

Note worthy are two unpublished observations of children and adults with low CD4+ counts from HIV AIDS. In both observations very low CD4+ counts of less than 400/ul (the clinical definition of AIDS) responded with rapid increases in CD4+ counts in a matter of months. Most if not all of the patients were on anti retroviral therapy (ART) concurrently. These drugs are shown to improve CD4+ counts but over a period of months to years and not in a few months as observed with TF and ART combined (5). The other clinical reports of note, involve persons with chronic Candida infections, the absence of normal T cell function and the ability of TF therapy to provide improvement of clinical and immunological parameters (Mobacken 1980, Littman 1977). The authors do suggest that antigen specific and non antigen specific actions of TF appear to be involved.

Several reports suggest that there is a component of TF and TF DLE that has hemopoetic properties. Barnet (1999) shows that TF DLE stimulates cytokines that hemopoetic properties. IL-3 is known to be hemopoetic. It has yet to be show to be elaborated in response to TF. Young horses infected with *S. equi* become lymphopenic, the degree to which is a mortality risk factor. In an intervention trial blood cell count data suggested that TF that was included in a complete nutritional supplement may have improved the lymphocyte count coincident with less severe lymphadenopathy and milder clinical disease (11).

As an experimental model radiation induced immune compromise and bone marrow suppression is very well documented. The use of TF DLE improved hemopoesis and the survival of irradiated mice. TF *in vitro* also appeared to complement the action of IL-3 on irradiated progenitor cells (Vacek 2000, 2002). Goleva (1999) demonstrated that TF improved immune rehabilitation and survival in irradiated mice that were subsequently challenged with a virulent strain of S. *aureus*.

Immune Balance and Modulation

The immune modulation or regulatory balancing of immune functions is one of the least appreciated properties of TF. Traditional physiological models regard immune system effectors as being either protagonistic or antagonistic with distinct chemical and biological properties. The concept that one moiety can have both functions in immune regulation has not been suggested until recently with the studies on the less than 2.5 KD fraction of TF (4). Yet as early as 1976 there was a clear suggestion that TF DLE has some regulatory function (Mueller 1976,Mischak 1979). They suggest that a fraction of DLE potentiates a DTH reaction to unique antigen by down regulating a suppressor substance from T suppressor cells (now referred as T reg cells). Holzman (1983) suggests there are both suppressor and inducer fractions in DLE. Since this was a skin test model it was not possible to discern if these were discrete fractions or simply attributes unique to the cell donors for the DLE. Lawrence (1986) proceeds to advance the notion that both suppressor and inducer fractions exist. Looking back this may have been the first suggestion of dual immune functions for TF DLE.

Rosso di San Secondo (1996) moved the concept of immune suppressor factor to the molecular level. They showed that a small peptide of less than 1KD inhibited lymphocyte transformation to the mitogen PHA, by blocking DNA synthesis in these cells. The peptide prolonged skin graft survival in mouse allografts. The researchers suggest this peptide is distinct from the 3.5 KD "suppressor" peptide described by Borkowsky (1983). Similarly, research on bovine colostral lymphocytes showed these T cells to be unresponsive to PHA, unlike those in circulation (2).

The first suggestion of differential regulation by DLE arose from the lab of Ojeda (2005). In response to pro-inflammatory components of gram negative and gram-positive bacteria, DLE reduced TNF alpha and increased IL-6 and 8 productions in activated monocytes. It also was shown to increase cAMP. In other studies DLE under different conditions DLE increased cGMP the antagonist.

This modulation may have a very pragmatic clinical effect. Sepsis will cause the elaboration of vasoactive cytokines the effects of which produce hypovolemic shock. Sonia Mayra (2007) was able to modulate this septic effect with DLE therapy.

Interesting and perplexing properties of TF ultra filtrates with a cut off of 10KW and with the smaller sub-fractions of 2.5 KD or less were observed in the assay of T cell competence. The Immuknow Test is an FDA diagnostic for evaluating the robustness of T cell immunity using a non-specific lectin stimulant PHA. The Immunknow test is used to titer the correct dose of immune suppressive drugs in transplant recipients while protecting some immune responsiveness to ward off viral infection.

TF and the smaller fractions had a dose response modulatory effect on the typically robust response to PHA in healthy adults. Paradoxically those persons that had lower CMI response to PHA had larger responses when the small fraction TF was added to the test system. Thus the smaller fraction appeared to have conditional or

situation response capabilities. Similarly in an antigen response assay similar to the Immunknow Test. When the TF sub-fraction was added with antigen it amplified the CMI response. In some persons with high CMI responses to an antigen the sub fraction lowered the response, further suggesting situation specific modulation (4).

More work needs to be conducted to ascertain the biology of this fraction. In conclusion its interesting to note that in humans maternal lymphocytes cross the placenta and impart immune information yet do not constitute any discernable graft versus host like reaction in the fetus or neonate (12). It may well be this modulating factor has this unique primary purpose and why colostral lymphocytes are non PHA responsive.

Summary

Transfer Factor (TF) host of molecules consists of those in the size of less than 10 KD have at least three distinct biological immune system functions. TF is produced by mononuclear cells of the immune system, in circulation and those found in organs like the spleen and lymph nodes. TF can be extracted and refined from these cells thru a process of cell disruption and ultra filtration using membranes with a 10KD nominal pore size. In nature free transfer factors can be found in colostrum and in egg yolk. Research data suggests that TF is very similar, if not identical across species lines.

Education

Transfer Factor has an immune system education function. Encoded in the variable region of the memory function molecule is the allosteric complementary peptide (ACP) that forms a three dimensional specific docking site within the T cell receptor. The molecule is a specific "foot print in the sand". This specificity allows for the highly accurate identification of microbial and other foreign antigens by the immune system while guarding against the formation of immune memory directed toward self-antigens. It is the basis of immune memory created from exposure to disease agents, vaccines or by passive transfer of the maternal memory thru colostrum or the egg yolk. TF is active through oral ingestion or parenteral injection. Naïve T cell receptors bind to the constant region of the TF memory molecule. Digestive enzymes, stomach acid or moderate heat do not alter its abilities.

Enhancement

The TF molecules are shown to be supportive and enhancing of immune function in and of themselves in a non-antigen specific manner. Confounding our

understanding they also appear to work in coordination with antigen specific factors in some aspects of immune function. In particular and perhaps most significant is the ability of the molecules to augment Natural Killer cell (NK) destruction of "self" cells that are altered by either viral infection or tumor transformation. This augmentation, confirmed in multiple assay formats, reconfirms this relationship of TF to enhanced NK cell function.

TF fractions increase cGMP in monocytes and this is associated with an up regulation of their function and may be the transformation of a resting monocyte to a so called "angry" mononcyte that is very active in phagocytosis and antigen processing. This processing is thought to be the manner in which microbial antigen becomes the template for the ACP TF. The presence of antigen TF facilitates blastogensis and cloning of T cells; this appears to be complementary and apart from antigen recognition. Antigen recognition and clonal expansion releases many cytokines including IL-2, a know T cell immunity enhancer. Thus some of the enhancement effects of TF may be via secondary mediators.

TF's function is not entirely limited to cell mediated immunity. The term CMI tends to ignore that fact that B Cells are immune cells that interact with T cells in the process of responding with antibody to immune challenge. Thus to find that TF augments antibody product through interaction with the T Helper cells is quite likely as the T Helper cells play role in the antibody class shift from IgM to IgG to IgA. Studies on this TF role have indeed shown this effect as well as an enhanced production effect on SIgA originating from Plasma cells.

The apparent ability of TF to accelerate immune reconstitution coincident with ART in AIDS patients is most interesting and promising. The immune mechanism must involve the non-specific functions of TF. However, the Retrovirus HIV may or may not have antigenic similarity to other bovine Retrovirus such that some cross reactivity may exist.

Balance

Immune response must have tight control mechanisms to conserve immune resources, prevent autoimmune reactions, and turn down immune reactions once the threat is passed. Several researchers show fractions that modulate. The work showed either enhancement or suppression, but not both in the same context. This may have been an artifact of the experimental design. More recently these small fractions in TF where shown situationally to both up and down regulate T cells from the same persons. These fractions may exemplify the elaborate command and control discretion of the immune system. More over the balance between the TH1 and TH2 Helper cells systems benefits from the direct and indirect abilities of TF and its smaller fractions appear to conditionally regulate proper and effective immune responses.

Table 1. List of Transfer Factor Search Terms

Category	Synonym
Education	Antigen Antigen specific Binding Cell mediated immunity Leukocyte migration inhibition Delayed Type Hypersensitivity or DTH
Enhancement	Natural Killer Cells Cytokines CD4, CD8, CD16 Phagocytosis IL 2, IL 12 TH1, TH2 Antibody Blastogenesis Skin test
Balance	Suppressor Modulation T Regulatory Cell Interleukins TH1, TH2

The selected references: (Name)(Year)

Education								
Year	Author	Title	Pub	Vol	No	Page	PMID	4Life #
1945	Chase, MW	Transfer DTH in Guinea pigs from sensitized donor leukocytes	Pro. Soc Exp Bio and Med	59		134		
1949	Lawrence HS	The cellular transfer of cutaneous hypersensitivity to tuberculin in Man	Pro. Soc Exp Bio and Med	71				
1955	Lawrence HS	The transfer in humans of delayed skin sensitivity to streptococcal M substance and to tuberculin with disrupted leukocytes.	J Clin Invest	34		219-32		1317
1957	Lawrence HS, Pappenheimer AM	Effect of specific antigen on release from human leukocytes of the factor concerned in transfer of delayed hypersensitivity.	J Clin Invest	36		908-9		1769
1969	Valentine FT, Lawrence HS	Lymphocyte stimulation: transfer of cellular hypersensitivity to antigen in vitro.	Science	165	897	1014-6	5804724	1326
1974	Ascher MS, Schneider FT, Valentine FT, Lawrence HS	In vitro properties of leukocyte dialysates containing transfer factor.	Proc Natl Acad Sci U S A	71	4	1178-82	4524630	1314

1975	Salaman MR	Studies on the transfer factor of delayed hypersensitivity. Effect of dialysable leucocyte extracts from people of known tuberculin sensitivity on the migration of normal guinea-pig macrophages in the presence of antigen.	Immunology	26	6	1069-80	4859507	1702
1976	Bell PH, Tao N, Keirns JJ, Colucci DF, Snedeker EH, Schaffer SA, Brockman JA.	Lymphocyte antigen sensitivity as a requirement for blastogenic response to transfer factor.	In: Transfer Factor: Basic Properties and Clinical Appliations. Academic Press, NY			705-8		1103
1976	Burger DR, Finke JE, Nolte JE, Vandenbark AA, Vetto RM	Human transfer factor: effects on lymphocyte transformation.	J Immunol	117	3	782-800	956653	1309
1976	Cohen L, Holzman RS, Valentine FT, Lawrences HS.	Leucocyte dialysates require precommitted, antigen-reactive cells to augment lymphocyte proliferation.	In: Transfer Factor: Basic Properties and Clinical Applications. Academic Press, NY			61-74		1038
1977	Lawton JW, et al.	Human transfer factor prepared by dialysis, ultrafiltration and gel chromatography: biological activity in local transfer of skin sensitivity.	J Immunol Methods	16	2	119-29	881554	2035
1977	Rifkind D, Frey JA, Petersen EA, Dinowitz M.	Transfer of delayed hypersensitivity in mice to microbial antigens with dialyzable transfer factor.	Infect Immun	16	1	258-62	68930	1691
1979	Wilson GB, Fudenberg HH, Bahm VJ.	Distinct components in dialyzable leukocyte extracts (DLE) have specific and nonspecific effects on cellular immunity as shown by leukocyte migration inhibition.	Trans Assoc Am Physicians	91	0	294-332	754397	1834
1979	Klesius PH	Bovine dialyzable transfer factor: Stimulation of antigen-specific leukocyte reactivity in C57/BL/6 mice.	In: Immune Regulators in Transfer Factor. Academic Press, NY			43-53		1111
1979	Schindler T, Baram P	The in vitro augmentation of antigen-induced proliferation of spleen cells obtained from human dialyzable leukocyte lysate (HDLL)-recipient mice sensitized to KLH.	In: Immune Regulators in Transfer Factor. Academic Press, NY			85-92		1115
1980	Borkowsky W, Lawrence HS	Deletion of antigen-specific activity from leukocyte dialysates containing transfer factor by antigen-coated polystyrene	Clin Res	28		550		1909
1983	Smith RA, Esa A, Stiff M.	Transfer of Salmonella resistance and delayed hypersensitivity with murine-derived transfer factor.	Infect Immun	36	1	271-6	7042572	1688
1984	Viza D, Rosenfeld F, Phillips J, Vich JM, Denis J, Bonissent JF, Dogbe K	Specific bovine transfer factor for the treatment of herpes infections.	In: Immunobiology of Transfer Factor. KAcademic Press, NY			245-59		1190
1986	Kirkpatrick CH, Rozzo SJ, Mascalli JJ	Murine transfer factor. III. Specific interactions between transfer factor and antigen.	J Immunol	135	6	4027-33	2415595	1790

1986	Kirkpatrick CH, Rozzo SJ, Mascalli JJ, Merryman CF	Murine transfer factor. II. Transfer of delayed hypersensitivity to synthetic antigens.	J Immunol	134	3	1723-7	2578518	6173
1989	Wilson GB, Shuler RR	Swine TGE specific Inducer (transfer factor): Clinical Efficacy.	Proc Sixth International Transfer Factor Soc.					
1989	Fayer R, et al.	Efficacy of bovine transfer factor to protect neonatal calves against experimentally induced clinical cryptosporidiosis.	J Parasitol	73	5	1061-2	3656003	1760
1989	Louie E, Borkowsky W, Klesius PH, Haynes TB, Gordon S, Bonk S, Lawrence HS.	Treatment of cryptosporidiosis with oral bovine transfer factor.	Clin Immunol Immunopath	44	3	329-34	3621678	1364
1990	Wilson GB, Poindexter C, Fort JD, Ludden D.	De novo initiation of specific cell-mediated immune responsiveness in chickens by transfer factor (specific immunity inducer) obtained from bovine colostrum and milk.	Acta Virol	32	1	6-18	2897772	1397
1994	Rozzo SJ, Kirkpatrick CH	Purification of transfer factors.	Mol Immunol	29	2	167-82	1542296	1896
1996	Micula I, Pistl J, Rosocha J.	Dialyzable leucocyte extract used in the prevention of Salmonella infection in calves.	Vet Immunol	32		113-24		8137
1996	Kirkpatrick CH	Structural nature and functions of transfer factors.	Ann N Y Acad Sci	685	0	362-8	8363241	2138
1999	Pizza G, Viza D, De Vinci C, Palareti A, Cuzzocrea D, Fornarola F, Baricordi OR.	Orally administered HSV-specific transfer factor (TF) prevents genital or labial herpes relapses.	Biotherapy	9	1-3	67-72	8993760	1012
2000	Kirkpatrick CH	Transfer factors: identification of conserved sequences in transfer factor molecules.	Mol Med	6	4	332-41	10949913	1286
ENHANCEMENT								

PubYear	Author	Title	Journal	Volume	Issue	Pages	PMID	4 life #
1974	Gallin JI, Kirkpatrick CH	Chemotactic activity in dialyzable transfer factor.	Proc Natl Acad Sci U S A	71	2	498-502	1974)	1315
1975	Sandler JA, Smith TK, Manganiello VC, Kirkpatrick CH.	Stimulation of monocyte cGMP by leukocyte dialysates. An antigen-independent property of dialyzable transfer factor.	J Clin Invest	56	5	1271-9	171284	1322
1976	Ascher, M. S., and Andron, L. A	Transfer factor (TF) in vitro nonspecificity of leukocyte dialysates that enhance lymphocyte proliferation to antigen	Fed. Proc		35	337	0	23867
1976	Krohn K, Gröhn P, Horsmanheimo M, Virolainen M.	Fractionation studies on human leucocyte dialyzates. Demonstration of three components with transfer factor activity.	Med Biol	54	5	334-40	994567	1268
1977	Littman BH, Hirschman EM, David JR.	Augmentation of 3H-thymidine incorporation by human lymphocytes in the presence of antigen and fractions of dialyzable transfer factor: a nonspecific phenomenon.	Cell Immunol	28	1	158-66	64313	1543

1978	Roda A, Roda E, Pizza G, Boucheix C.	Human transfer factor produced in vitro increases antibody titers in rabbits.	N Engl J Med	298	11	629	628380	1867
1980	Mobacken H, Hanson LA, Lindholm L, Ljunggren C.	Transfer factor in the treatment of chronic mucocutaneous candidiasis: a controlled study.	Acta Derm Venereol	60	1	51-5	6153834	1416
1979	Ascher MS, Andron LA	Transfer factor in vitro: nonspecificity of components that enhance lymphocyte proliferation to antigen.	Clin Immunol Immunopathol	12	1	72-81	84724	1606
1979	Salaman MR, Sargent IL, Sijivic VS.	Transfer factor as an adjuvant for antibody production in the mouse.	In: Immune Regulators in Transfer Factor. Khan A, Kirkpatrick CH, Hill NO, Eds. Academic Press, NY			661-5	0	1164
1982	Lin MS, et al.	Partial reversal of radiation-induced immunosuppression by T-lymphocyte lysate.	Immunology	47	3	489-96	6752006	1698
1989	Doelker I, Voetsch W, Anderer FA	Activation of antitumor cytotoxicity of human blood mononuclear cells by a basic factor from dialysable human-leukocyte extract.	Anticancer research	9	6	1915-20	2627139	2142
1989	Hamprecht KH, Vötsch W, Anderer FA	A dialysable acid factor from human leukocyte extracts activates tumor cell lysis mediated by human monocytes and natural killer cells.	Onkologie	12	3	120-7	2668834	22147
1999	Barnet K, et al.	DLE Increase Stimulatory Effect Of Cytokines On Hemopotesis	In: Proceedings of the XIth International Symposium on Transfer Factor. March 1-4, 1999.				0	20065
1999	Goleva EG, et al.	Transfer Factor Of Cell-Mediated Immune Response Rehabilitation Activities In Irradiated Mice	In: Proceedings of the XIth International Symposium on Transfer Factor. March 1-4, 1999.				0	20054
2000	Vacek A, Hofer M, Barnet K, Cech K, Pekárek J, Schneiderová H	Positive effects of dialyzable leukocyte extract (DLE) on recovery of mouse haemopoiesis suppressed by ionizing radiation and on proliferation of haemopoietic progenitor cells in vitro.	Int J Immunopharmacol	22	8	623-34	10988357	2015
2002	Vacek A, Hofer M, Hromas J, Luksíková E, Svoboda J, Schneiderová H	Hemopoiesis-stimulating effects and enhanced survival of irradiated mice after peroral or intraperitoneal administration of ultrafiltered pig leukocyte extract (UPLE, IMUNOR).	Immunopharmacol Immunotoxicol	24	4	651-64	12510796	2124
MODULATION								
PubYear	Author	Title	Journal	Volume	Issue	Pages	PMID	4 Life #
1976	Mueller-Eckhardt C, Ritts RE	Inhibitory activity of medium-dialyzed transfer factor on lymphocyte blastogenesis.	Blut	32	5	353-60	1268337	1493

1979	Mischak RP and Spitler LE	Modulation of suppressor activity by treatment with dialyzable leucocyte extract.	In: Immune Regulators in Transfer Factor. Academic Press, NY			5-13	0	1108
1983	Borkowsky W, Lawrence HS	Antigen-specific suppressor factor in human leukocyte dialysates suppresses in vivo footpad reactivity in immunized BALB/C mice.	In: Immunobiology of Transfer Factor. Academic Press, NY			189-96	0	1185
1983	Holzman RS, et al.	Isolation and purification of antigen-specific inducer and suppressor factors from pooled leukocyte dialysates of unselected donors by affinity adsorption.	In: Immunobiology of Transfer Factor. Academic Press, NY			117-25	0	1180
1984	Gottlieb AA, Farmer JL, Matzura CT, Hester RB, Rosenberg JS.	Modulation of human T cell production of migration inhibitory lymphokines by cytokines derived from human leukocyte dialysates.	J Immunol	132	1	256-60	6361122	1791
1986	Lawrence HS	Characterization of inducer factor and suppressor factor in T cells dialysates.	In: 8th Congress on Immunology, Canada	0			0	8443
1996	Rosso di San Secondo VE, Aniasi A, Piccolo G. Montecucchi PC, Sirchia G.	Influence of a DLE-extracted lymphocytic suppressor factor on CsA-induced immunosuppression.	Biotherapy	9	1-3	159-62	8993775	1027
2005	Ojeda MO, van't Veer C, Fernández Ortega CB, Araña Rosainz Mde J, Buurman WA	Dialyzable leukocyte extract differentially regulates the production of TNFalpha, IL-6, and IL-8 in bacterial component-activated leukocytes and endothelial cells.	Inflammation research : official journal of the European Histamine Research Society.	54	2	74-81	15750714	2134
2007	SONIA MAYRA PEREZ-TAPIA, INES LOPEZ-ISLAS, MARISOL DE LA FUENTE-	Use of dialyzable leukocyte extracts (DLE) in patients with severe sepsis	J Immunology	178		49.35	0	4125

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