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Review Article

Clinical Experience of Thymic Regeneration with Thymus Extracts, Thymic Peptides and Stem Cells in General Medicine, Oncology and Anti-Aging Medicine: A Review

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Abstract

Thymus plays a crucial role in immune system development and T-cell maturation. With aging, thymus activity declines, which leads to a weakened immune system and an increased risk of infections and cancer. In recent years, thymus extract has gained attention as a potential treatment for cancer and anti-aging. Studies have suggested that thymus extract can stimulate the production of T-cells and enhance immune function, which may lead to improved outcomes in cancer patients. It may also have anti-aging effects by reducing inflammation and improving immune function. In addition, thymus extract has been reported to reduce the side effects of chemotherapy and radiation therapy in cancer patients.

Keywords: Thymus; Peptides; Immunotherapy; Stem cells; Precursor stem cells; Cell therapy; Immunity; Cancer; Anti-aging; Thymic regeneration; Immunosenescence

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Introduction

There are two types of immunity: innate and adaptive. The adaptive immune system can be further divided into cellular and humoral types. B lymphocytes that create antibodies to particular antigens are part of humoral immunity, whereas specialized immune cells provide cellular immunity. T helpers, T suppressors, T killers, and T cytotoxic cells are the immune cells responsible for the cellular immunity. Cellular immunity is primarily mediated by the T lymphocytes maturing in the thymus gland and is essential for preventing bacterial, fungal, and viral infection, preventing aging, and maintaining the population of neoplastic cells [1-3].

The bone marrow is the place of genesis for the immune cells of the myelopoietic cell lineage, which contains the T lymphocytes. T1 cells are immature thymocytes that express the CD1 marker in bone marrow. T1 grows and matures, before migrating out the bone marrow, losing their CD1 cell surface marker, and acquiring a CD3 lymphocyte cell surface marker, becoming T3 cells. The T cell changes into a T-helper/inducer cell and add a CD4 marker to its cell surface to become a T4 cell, while T3 cells come into contact with an antigen suitable for a cellular immune response. Some T cells develop into cytotoxic or suppressor cells that express CD8, which can also be known as T8 markers. Once T cells have made a commitment to an antigen, they are ever-vigilant and committed to that antigen [4-6]. The thymic hormones and their subsequent cell products, interleukins and interferons, control the various T cells' maturation, development, antigen commitment, proliferation, and cytotoxic activity [7,8].

Products containing thymus extracts have become an important component of the treatment of several types of cancer because the thymus is one of the main immunocompetent organs responsible for the development of the cellular aspect of immune response and thymus hormones/peptides account for the maturation of T-lymphocytes [9-11]. Lymphoid tissue-specific cell extracts, which support tissue reconstitution and remodeling, are used in therapeutic regeneration strategies. Thymus therapy, also known as live cell, fresh cell, and cell therapy, is a form of cellular therapy in which the body is given injections of fresh fetal animal cells. The thymus therapy's development and commercialization have gone through various stages [12-15].

Thymus therapy is administered for three main purposes: to treat disease, particularly Alzheimer's disease, epilepsy, and Down's syndrome; to rejuvenate or restore youthful appearance and the function of skin, libido, and body organs; and, in what is probably the least common application, to enhance immune protection against toxicity produced by chemotherapy [12,15-20].

Commercially available thymus extracts contain varying amounts of three different active hormones isolated from the thymus: thymulin, thymopoietin and thymosin-alpha-1 [11,21-23]. Two other partially purified active substances, thymosin, also contain constituents of lymphocytes and epithelial cells in addition to one of the thymus peptides [11,21]. An oligopeptide (fraction V) with a molecular weight greater

than 3000 Da is the shortest active thymus fraction producing discernible activity. Since it is challenging to completely remove all of the thymus hormones and other active fractions from the stroma and parenchyma of thymus tissue, commercial preparations, whether liquid or solid, typically contain at least one of the three thymus hormones [23].

Thymus extracts have been used in human trials for more than ten years threating a variety of chronic illnesses and infections. These positive clinical results have been associated with the cellular immunity provided by T lymphocytes (helper/inducer, suppressor, cytotoxic, NK cells, K cells, and macrophages), which suggests that thymus extract affects these cells' functions by regulating their production, activation, and maturation [9,21,24,25]. The literature gives an account of thymus extract being used either orally or as injectables, by itself or in combination with other therapeutic agents to treat various ailments.

The majority of the advancements in thymus therapy have been in the cellular branch of immunity involving T lymphocytes, including T helper, suppressor, cytotoxic cells, NK cells, and macrophages, despite the paucity of data on modifying the function of B lymphocytes. The generation, maturation, and activation of T lymphocytes and macrophages have been demonstrated to be modulated by thymus extracts, and the conversion of immature thymocytes to non-dedicated T cells in human bone marrow has also been shown to be accelerated. Thymus extracts have been demonstrated to significantly boost the number and activity of T helper and T suppressor cells in more developed T cells [10,11,12,26].

Role of Thymus Involution in Immunosenescence

Immunosenescence lowers innate and adaptive immunity, impairing response to pathogens and vaccines and increasing susceptibility to tumor development due to decreased surveillance of formed neoplastic cells and their earlier destruction as well as autoimmune diseases [27-31]. Every aspect of aging that occurs can set off a fatal immunosenescence. Thymic involution or atrophy, which is characterized by a loss of T lymphocyte variety and efficiency as well as a steady decline in thymic cellularity and tissue organization, is essential to this process [32-35].

Thymic involution, which occurs when adipose tissue replaces thymic epithelial tissue and decreases T cell export from the thymus, affects humans, like the vast majority of vertebrates. Human thymic involution starts at 1 years of age, and it is thought that the rate of thymic T cell production declines exponentially over time, with a half-life of approximately 15.7 years [32,34]. The declining production of new naive T cells is thought to be a significant component of immunosenescence, the age-related decline in immune system function. The main hallmarks of immunosenescence are increased incidence of infectious diseases and cancer with age [36-38]. There are numerous elements, both internal and environmental, that affect how effective and adequate immune responses are. Nutritional status, physical trauma, surgery, infections, antibiotics, chemotherapy, radiation, corticosteroids, an unfavorable environment, and substance addiction are a few of the main extrinsic factors that contribute to immunodeficiency. A major intrinsic factor in immunodeficiency is aging, which is accompanied by chronic systemic diseases [1,15].

Role of Thymus Involution in Aging

The thymic involution with aging ultimately results in a reduction in thymic naive T cell production and subsequently a narrowing of the peripheral T Cell Repertoire (TCR), impairing the diversity and efficiency of T lymphocytes [15,33,34]. Additionally, this results in the release of senescence-specific markers like CD57 and a decrease in receptors like CD62L and CCR7, which reduces cellular responses to antigens and the migration of functional cells to the appropriate sites [38-42]. Age-related autoimmune disease progression is another aspect of thymic involution. Negative selection causes naive T cells to respond negatively to themselves at a specific location in the thymus through interactions with Thymic Epithelial Cells (TECs) and thymic dendritic cells [42]. Age-related loss of these thymic cells impairs their capacity to mediate this central tolerance, increasing the likelihood that self-reactive T cells will be discharged in the peripheral [35]. Thymopoiesis is characterized by the gradual differentiation of pro-T cells, the most primitive of which is the Initial T-lineage Progenitor (ETPs), a direct descendant of the circulating bone marrow-derived progenitor [36,38].

Therapeutic Strategies in Reversing Dysfunction of Thymus

To improve a potent adaptive immune response against pathogens and tumors while preventing autoimmune disease, a diverse but self-tolerant T cell repertoire must be developed. Thymus is extremely sensitive to various insults. Immunosuppression may be caused by aggressive and ablative treatments such chemotherapy, radiation, and immunotherapy using antibodies (for example, to treat hematopoietic cell transplants or thymic graft versus host disease, or the GVHD). These elements create a catalyst that speeds up aging and the immunosenescence process [2,3,8,15,37]. Thymic involution differs from organ aging in that it reduces the thymus' capacity to recover from acute injury [33]. Consequently, there is a growing need for exogenous methods that can repair or regenerate the thymus. The most significant causes of immunological aging, thymic degeneration, increased mortality, and pathogenic co-morbidities are listed below.

Ablative therapies

While it was traditionally thought that thymic stromal cells were resistant to damage from chemotherapy or radiation, there is now considerable evidence to suggest that such agents can also damage the thymic stroma by influencing T cell immunodeficiency [43,44]. Thymic Epithelial Cells (TECs) expressing the highest levels of MHC Class II are particularly vulnerable to the effects of chemotherapy, especially those located in the marrow (mTECs) [44]. The homeostatic increase of functional peripheral clonal T lymphocytes and their variety can eventually return after chemotherapy treatment; however, elderly patients may take years, if ever, to do so compared to young patients [44,45].

Steroid hormones

Allograft rejection, allergic and inflammatory disorders, GVHD, and lymphoid malignancies are just a few of the conditions for which glucocorticoid hormones act through the nuclear Glucocorticoid Receptor (GR). These conditions also include autoimmune diseases, allergic and inflammatory disorders, GVHD, and lymphoid malignancies. Immunosuppression can also result from increased amounts of endogenous glucocorticoids, which are produced by stress, hunger,

infection, and Cushing's disease. The connection between the hypothalamic-pituitary-adrenal axis and neuroendocrine stress is well understood. Adrenocorticotrophic (ACTH) overload occurs first, then sex hormone depletion and inflammatory stimulation [46-49].

Adrenal fatigue and negative feedback on the hypothalamus-pituitary-adrenal axis result in chronically released glucocorticoids, which have a long-lasting immune-incompetence effect, when stress becomes chronic. In this setting, the tendency to infections, allergies, autoimmunity, and other inflammatory illnesses increases due to thymic atrophy brought on by neuroendocrine-immunological aging. Increased levels of the sex steroid hormones testosterone, progesterone, and estrogen also cause thymic involution by acting through their nuclear receptors. When the pace of thymic involution grows quickly during puberty, their effect is most visibly present. Sex hormones can affect lymphoid differentiation and the amount of T cell progenitors present in the thymus through a variety of mechanisms [15,48,49].

Role of Thymus Therapy in Treatment of Various Diseases

Cancers

Hematological Malignancies

Hematological malignancies are a group of heterogeneous conditions of cells arising from the bone marrow and the lymphatic system, which are broadly classified into leukemia, lymphoma, and plasma cell neoplasms [50]. Based on the subtype of the haematological malignancy involved, the etiopathogenesis, incidence, and mortality are determined. Increased Disability-Adjusted Life-Years (DALYs) among these disorders have been observed during the past few years, calling for serious consideration of an alternative and efficient treatment approach.

Chronic Lymphocytic Leukemia (CLL)

In a particular study carried out among 20 patients diagnosed with early and untreated chronic lymphocytic leukemia (CLL), thymic peptide therapy was shown to decrease the number of total lymphocyte count while increasing erythrocyte rosetting. An increase in the acid phosphatase lysosomal activity of the lymphocytes was also noted with a concurrent increase in serum immunoglobulin levels, reticulocyte counts and hemoglobin levels. Finally, results showed the normalization of skin sensitivity using a tuberculin test, which denotes well-functioning cell mediated immunity [51,52].

Hodgkin's Lymphoma

Previously called Hodgkin's disease and later Hodgkin lymphoma, this disease is a relatively rare monoclonal lymphoid neoplasm with a very good prognosis and cure rate. It is estimated that approximately 11% of all diagnosed lymphomas are Hodgkin's with an incidence of 2.6 cases per 100,000 Americans [53].

Hodgkin's lymphoma's specific cause is unknown, however several factors, such as underlying autoimmune disorders, immunocompromised states, and the Epstein-Barr virus, have been associated with a higher likelihood of acquiring the disease. Depending on the stage of the disease, the main forms of treatment include chemotherapy and limited involved-field radiation therapy (IFRT) [54]. A study involving 10 patients with advanced Hodgkin's lymphoma examined the effectiveness of thymus extract in treating the condition. Even in patients with a histologically lymphopenic appearance, the results demonstrated an increase in lymphocyte counts. Also, findings demonstrated that cellular immunity and hematological parameters were enhanced, and trials of thymic peptide theapy in patients who also had mycobacterial or viral infections were deemed to be highly beneficial [52,53]. Explaining the possible mechanism of action, authors suggested that the advanced state of the disease is characterized by the patients' lymphopenic and hypothymic states, and that thymus therapy offers a new hope of treatment, possibly as an adjuvant to the existing conventional treatment regimen.

Non-Hodgkin's Lymphoma

Another form of cancer that develops in the lymphatic system is non-Hodgkin's lymphoma. In order to determine the therapeutic effects of TP-1 in 134 patients with non-Hodgkin's lymphoma in stages 2 to 4 or stage 1 with bulky disease and no prior treatments, the patients ranged in age from 13 to 75. Patients were randomized and 68 were treated with TP-1 alone while remaining patients received both the chemotherapy and TP-1. For patients receiving the Pro-MACE-CytaBOM regimen of prednisone, methotrexate, cyclophosphamide, etoposide, cyclophosphamide, bleomycin, and vincristine, TP-1 was administered intramuscularly on days 22 to 28 and on days 50 to 57 and 77 to 85 of each 28-day cycle of chemotherapy. For those receiving the MACOP-B regimen of methotrexate, clotrimoxazole (BactrimTM) and either fluconazole or ketoconazole were given daily doses to the control and intervention groups [55].

Results showed a higher complete remission rate of the disease among the trial group (59.1%) compared to the control group (42.6%) and similarly a lower partial remission rate. Patients diagnosed with intermediate-grade cancer who were under 60 years old, had good hemoglobin levels, and were diagnosed with the disease were more likely to experience complete remission. According to the study, individuals who had chemotherapy and had healthy bone marrow recovery could benefit from adding thymic treatment to their current standard chemotherapeutic regimen. These patients also got daily doses of clotrimoxazole (BactrimTM), ketoconazole, or fluconazole [55].

Lung Cancer

Bronchogenic carcinoma, often known as lung cancer, is a group of highly aggressive cancers that develop in the bronchi or lung parenchyma. Compared to other major cancers, such as colorectal, breast, pancreatic, and prostate, lung cancer claims more lives each year. Although tobacco use and smoking are known to cause lung cancer, additional variables have also been linked to the disease, including radon gas exposure, asbestos exposure, particularly that linked to pneumoconiosis, extended exposure to poor air quality, and chronic infections [56]. The main subtypes of lung cancer include squamous cell lung carcinoma, adenocarcinoma, large cell anaplastic carcinoma (non-small cell lung carcinoma) and small cell lung carcinoma [56]. The treatment of lung carcinoma depends upon the stage at diagnosis as well as the type of carcinoma, the mainstay being chemotherapy, radiotherapy, and surgical resection [56].

In previous clinical trials, thymus therapy has been used to halt the progress of the disease as well as to buffer the side effects of conventional therapies. It has been demonstrated that chemotherapy decreases T and B lymphocyte counts as well as those of Natural Killer cells, cytotoxic, and suppressor cells. As discussed earlier, these cells are pertinent defenses against neoplastic cells. In a clinical trial among 12 patients suffering from either undifferentiated or squamous cell carcinoma, the administration of thymic peptide therapy alone twice

weekly for 10 weeks showed marked clinical improvements in 10 patients. Results also showed the inhibition of local tumor expansion as well as reduced mediastinal metastasis. Partial regression of tumor bulk was seen in 3 patients. Importantly, the 6 months of the trial group of participants' survival rate was 42% in contrast to the control group survival rate of 7%, which only received symptomatic treatments [57].

In a different study, individuals with small cell carcinoma who were receiving six cycles of chemotherapy also received thymostimulin (TP-1). On days 7 through 14 of the 3 to 4 week chemo cycle, 15 patients in the intervention group received TP-1 1 mg/kg intramuscularly, and another identical dose was administered twice weekly at the conclusion of the 6 week cycle. In comparison to just 1 patient in the control group, the data showed that 7 patients had complete remission. Similarly, just 4 patients in the intervention group had illness progression, compared to 7 in the control group, according to the results. The treated group's mean survival time was also significantly longer, and side effects from the chemotherapy were seen to be less severe overall, including neutropenia severity. The patients in the intervention group's increased quality of life was also demonstrated by the results [15,57]. Similar trials among patients with non-small cell as well as bronchogenic carcinoma have shown corroborating clinical outcomes.

Breast Carcinoma

Breast cancer, the second-leading cause of cancer-related deaths each year, accounts for about 10% of newly diagnosed cancer cases. It is projected that 1 in 1000 men may develop breast cancer in their lifetimes, despite the fact that the disease was formerly thought to only affect women. The aim of treatment is to lessen the likelihood of metastasis and local recurrence. In addition to systemic methods including chemotherapy, hormone therapy, and targeted therapy, treatment options may include surgical excision and radiotherapy [58].

In a sample of 85 patients who were receiving chemotherapy and had advanced breast cancer and a history of mastectomy, the effects of thymus treatment were examined. Following randomization of the patients, the trial group received thymostimulin in addition to their chemotherapy regimen while the control group only received chemotherapy. The intervention group's leukopenia severity was almost half that of the controls', according to the results, and they also had a lower incidence of infection [59]. In a comparable trial, it was discovered that thymus extract given intramuscularly twice weekly for four to six weeks improved clinical outcomes in 26 patients with breast cancer who had undergone mastectomy with axillary clearance one to two years prior to the study. Disease activity was monitored using the Carcino-Embryonic Antigen (CEA) levels on regular intervals.

Results showed a reduction in serum CEA levels among approximately 70% of the intervention group compared to approximately 47% of controls. Noting the safety profile of thymus therapy, with no side effects observed, authors stated that immunological treatment should be considered as a mainstream treatment modality for breast cancers [60]. According to several related research, adding thymus therapy to a standard treatment plan improves clinical outcomes, survival rates, and infection levels [15].

Gastrointestinal (GI) Tract Carcinoma

The financial and medical costs of gastrointestinal cancers are significant worldwide. According to estimates, 4.8 million new cases of gastrointestinal (GI) cancer are reported each year, accounting for around 26% of all cancer diagnoses and 35% of cancer-related fatalities. They include the five primary gastrointestinal malignancies, which have origins in the esophagus, stomach, liver, colon, and pancreas [61]. In one trial, thymic peptide therapy was administered to 50 patients with inoperable colorectal cancer, and the clinical results were closely monitored. Findings revealed that these individuals had improved laboratory immunological markers and clinical outcomes, demonstrating greater cell-mediated immunity. Twelve of these patients' histopathological data suggested tumor regression in conjunction with an improved host response to the tumor [62]. A 15 year longitudinal study involving 457 patients with GI or breast cancers who were given thymus extract showed relatively fewer post-operative complications, enhanced wound healing and notably, increased survival time compared to those who weren't subjected to the thymus extract [63]. The use of thymus extract in colorectal patients led to positive results, as well as post-operative and post-chemotherapy benefits, according to numerous studies of a similar nature [64].

Hepatocellular Carcinoma

The most frequent primary liver cancer is hepatocellular carcinoma, which is also the tenth most common cancer in America. In Eastern and Southern Asia, Middle and Western Africa, Melanesia, and Micronesia/Polynesia, this illness affects more men than women [65]. There have been a few studies in this area, and one pilot study found that using thymostimulin (TP-1) alone, without receiving any other conventional treatment, caused 50% of the intervention group to experience tumor regression. Theoretically, the Kupffer cells release considerable amounts of tumor necrosis factor-alpha and interleukin 1 alpha & 6 under the influence of thymostimulin, which have immunomodulatory effects akin to host defense mechanisms [66].

Role of thymus therapy in anti-aging medicine

A variety of immunotherapies, including vaccines, which includes both preventative and therapeutic, monoclonal antibodies, cytokines, and cellular immunotherapies, are being developed quickly, excitingly, and with great potential [15]. They are altering how we treat a variety of illnesses, particularly cancer. Since the aging process involves numerous metabolic, hormonal, and immunologic systems, these discoveries can be used to treat immunosenescence and other degenerative diseases as well as age-related immunological dysfunction. Alternatively, it has been suggested that immune system effectiveness declines with aging, which is now confirmed to occur. One theory is that the ratio of T cells to B cells varies over time with negative implications on immunological function [67].

As the immune system reaches its peak in adolescence and declines in function as people age, diseases including cancer, infections, and degenerative illnesses can develop or take on new forms [68]. Age has a direct relationship to how much immune activity declines. According to immunological studies on the aged, certain people have a tendency to develop autoimmune diseases as they age. Autoimmune illnesses are triggered by aging and decreased cellular immunity brought on by impaired thymus function, according to research [46].

It has been proposed that immunotherapy using thymus extract therapy can lengthen life, especially in older people, by reducing chronic disease, slowing accelerated aging, and preventing premature aging [69]. Thymic peptide therapy can be given intravenously for at least three weeks, varying from twice weekly to daily. A longer

course of therapy, lasting anywhere from six months to a year, may be required for serious instances, including malignancy. It is feasible to wait three to six months before starting the second cycle of thymus therapy in chronic cases [68].

After three weeks of treatment, the immunological markers indicated that the immune functions in the elderly had returned to normal. Dr. Sandberg observed that thymus therapy is effective in addressing a wide range of indications in geriatric patients over the course of several years of clinical experience. With noticeable improvement and the healing of chronic illnesses occurring 4–6 weeks after the completion of the therapy, his therapeutic success rate in the group of patients under examination is 80–90%. All patients were watched and followed up on as outpatients for six months, and the majority of them showed signs of successful healing. After six months, further therapy with whole thymus extract was recommended in the most challenging cases that featured treatment resistance [15].

Thymus therapy is gaining popularity today for the prevention, treatment, and lengthening of life in patients with middle-aged and older diseases, such as autoimmune disorders, heart failure, arteriosclerosis, and circulatory disorders that impact the major organs. A stronger immune system increases older people's resilience to harmful environmental impacts and intrinsic variables that hasten immunosenescence and the aging process, which delays aging and lowers the risk of morbidity [15,68].

Commercially Available Thymus Peptide Preparations

Thymosand

Due to their enzymatic degradation processes, which are impacted by numerous factors and affect the bioavailability of thymus preparations containing thymus fractions and thymus peptides of various amino acid chain lengths, a precise assessment is not possible (including genetics, metabolism, enzyme activity, immune status). Their bioavailability varies depending on how they are administered (e.g., subcutaneous vs intramuscular). It is possible to radioactively label thymic peptides that have been biochemically described, but it is unclear whether the isotopes will stick to the entire molecule or whether they will already be connected to specific amino acids in the organism [15].

Thymosand, a true complete extract from calf thymus that is cell-free, sterile, and pyrogen-free, is one of the commercially available thymus preparations. The protein solution contains both the structurally non-structured, biologically active low-molecular substances (such as amino acids and lower peptides) and the high-molecular polypeptides and proteins (such as enzymes) in the thymus-specific composition. It is produced using a specialized cleaning and extraction process in the form of a colloidal solution as an aqueous thymus extract at physiological concentration. Thymosand is non-pyrogenic, non-immunogenic, sterile, and free of preservatives [70].

After standardisation to a total protein-peptide content of 1.0 mg/ml is completed, a considerable number of the constituents can be precisely identified using polyacrylamide electrophoresis (SDS). Thymosand exhibits a comparatively high percentage of proteins with bigger molecular masses of the following molecular weights: 5,000Da, 13,000Da, 31,000Da, 36,000Da, 43,000Da, 45,000Da, 66,000Da, and 90,000Da, as expected, when the SDS-PAGE separation is examined. Thymosand has been found to contain a variety of enzymes, including transaminases, lactate dehydrogenases, alkaline and acid phosphatases, glucose-6-phosphate dehydrogenases, esterases, and creatinine kinase, in addition to these immunomodulating thymus proteins. The immune stimulating activities of up to 140% have so far been in the rosette test and has been confirmed in the phagocytic activity of human monocytes [71]**.** Thymus extracts for injection have been commercially available for years. This preparation, a specially purified extract from calf thymus, was approved by the Federal Health Office under approval no. 3156.00.00 on July 17, 1983 according to the 2nd Medicines Act of 1976 [72].

Another 274 patients from the Schwarzwald Private Clinic Obertal were treated with Thymosand® for 3 weeks. The purified thymic peptide fraction was administered on average at a dose of 500 µg per injection for 15 days. Most patients were in the age group of 50 - 80 years (86%). The main diagnoses were immunodeficiency (53%), rheumatic diseases (52%), followed by respiratory diseases (35%), often associated with age-related comorbidities (hypertension, cardiovascular disease, metabolic disorders); 25% had a reduction of tumor volume. Results from the clinical and immunocytological laboratory findings showed a significant improvement of the clinical outcomes and decrease of pathological laboratory values of the immune status (Immunological side effects analysis of the Thymus extract Thymosand, Project No.:5-07). Particularly noteworthy is the relative and absolute increase in cytotoxic T lymphocytes ($p < 0.001$), which has not yet been observed with other drugs (Mitogenic costimulation of lymphocytes. Project No.:9-031/89). No Thymosand-related adverse events or treatment discontinuations were reported (Single dose toxicity test of Thymosand in mice. Project No.:10-01-2672/00-93). The therapeutic results are consistent with the immunological research results in vitro and in vivo as per mouse models (Acure intravenous toxicity in rat with Thymosand. Project No.:1-4-235-89) [15].

The therapeutic range and the very good tolerability of Thymosand have been repeatedly confirmed by the doctors at the Black Forest Medical Resort Obertal (formerly Schwarzwald Private Klinik Obertal). A follow-up procedure with 5–10 Thymosand injections should typically be carried out 4–6 months after the initial therapy. Thymosand injections range from 5 to 10, and therapy intervals are tailored to the particular situation. A repeated therapy once a year is recommended for patients over the age of 50. Treatment intervals of six months are frequently needed in chronic illnesses that are severe. The doctors at the Black Forest Medical Resort Obertal (previously Schwarzwald Private Klinic Obertal) have found that 15 to 20 separate Thymosand injections have shown to be particularly effective [15].

MitoOrganelles "Thymus"

Stellar Biomolecular Research has participated in the formulation and generated experimental and clinical data on recommended protocols of administration of various preparations of thymus peptides. Nanopeptides, known as Nano Organo Peptides (NOP), produced by Stellar Biomolecular Research are commercially available under the MF+ product range. Mito Organelles™ (MO) peptides are biologically extracted mixtures of cellular peptides that have predominantly mitochondria-specific functions [73]. Although cells of different organ systems have similar functions, variations in cellular functions between organs creates the differential expression of peptides, which can be utilized for various therapeutic purposes. MO peptides are

organ-specific extracts that are aimed at revitalizing and rejuvenating mitochondrial activity, thereby regenerating cells and organisms as a whole [74,75]. These are suitable for both sublingual and intramuscular administration owing to their relatively small molecular size and weight [76]. The recommended frequency of administration varies from three to five times per week. The duration of one cycle of thymus therapy should be a minimum of four months with short breaks and can be repeated two to three times per year. The recent improved formulation of nanopeptides with increased content of biologically active thymus peptides can be administered three times per week with the same duration. The "Mito Organelles" peptides also produced by MF+ has a higher concentration but also has a higher molecular weight than nanopeptides. This significantly increases the therapeutic efficacy of the thymus therapy, but makes intramuscular administration the preferred route for the "Mito Organelles".

The Mito Organelles (MOs) range of products (drugs) were launched in 2016. Herein, we report the previously unpublished experience of the use of the MO "Thymus" peptides since 2017 till 2020. During the four-year term between 2017 and 2020 26 patients volunteers used who altogether used 107 boxes (10 vials per box) of the MO "Thymus" peptides.

The main indications for the clinical application of the MO "Thymus" are the following:

- Complementary immunotherapy concurrent or post chemotherapy in cancer patients
- Autoimmune disorders, including rheumatoid arthritis, SLE
- Dermatological disorders, such as acne, eczema, psoriasis
- Immunodeficiency of various cause, otherwise not specified

Among the 26 volunteers who received the MO "Thymus" in 2017-2020, in 20 human subjects there were notable improvements reported – 76.9% (previously unpublished data).

Based on the feedback from the medical professionals who prescribed the MO "Thymus" as well as based on the feedback and testimonials from the patients, the working group that created this report was able to list down the following benefits observed:

- None of the patients with cancer, who underwent chemo or radiotherapy, and received the MO "Thymus" peptides as a part of the complementary immunotherapy, were reported to develop septic complications during the chemo or radiotherapy while receiving MO "Thymus" peptides;
- No cases of neutropenia were observed among the mentioned patients as well
- Reduction of pain and joint swelling in patients with SLE and rheumatoid arthritis
- Reduction of the intensity and severity of the cutaneous lesions in patients with acne
- Reduction of the intensity and area of the spread of the eczema
- Rapid reduction of wetness of eczema lesions
- Prolong remission periods in patients with dermatological disorders eczema and psoriasis
- Reduction of the dose of corticosteroids both topical and systemic in patients with eczema and autoimmune disorders (SLE and RA)
- Improved white cell count in immunodeficient patients
- Absence of secondary infections and septic complications in the patients who received the MO "Thymus" peptides
- Reduction or disappearance of fatigue
- Increased physical endurance and strength

Discussion and Further Considerations Regarding Thymic Regeneration

Thymus regeneration, stem cells, and tissue engineering are three interrelated topics in the field of regenerative medicine. The thymus gland is responsible for the production and maturation of T-cells, which play a vital role in the immune system. However, the thymus gland undergoes significant involution or atrophy with age, which can result in a weakened immune system. Stem cell-based therapies and tissue engineering approaches have emerged as promising approaches to thymus regeneration.

Thymus transplantation has been successfully used in patients with severe combined immunodeficiency (SCID), a rare genetic disorder that results in a complete lack of T-cells. However, the availability of donor thymus tissue is limited, and the risk of graft-versus-host disease (GVHD) remains a significant concern [77].

Stem cell-based therapies have shown promise in preclinical studies for thymus regeneration. Thymic epithelial stem cells, hematopoietic stem cells (HSCs), and induced pluripotent stem cells (iPSCs) have all been investigated as potential sources of cells for thymus regeneration. Several studies have demonstrated the ability of thymic epithelial stem cells to regenerate thymic tissue and restore T-cell function in animal models [80]. HSCs have also been shown to differentiate into T-cells in the thymus, and studies have demonstrated their ability to regenerate thymic tissue and restore T-cell function in animal models [78,79]. iPSCs have been shown to differentiate into functional thymic epithelial cells and T-cells in vitro and in vivo, offering a potential source of cells for thymus regeneration [80].

Tissue engineering approaches to thymus regeneration involve the use of biomaterials and three-dimensional (3D) printing technologies to create a scaffold that can support the growth and differentiation of thymic epithelial cells and T-cell progenitors. These approaches have shown promise in preclinical studies, with evidence suggesting that 3D-printed scaffolds can support the development of functional thymic tissue in vivo [81]. One study showed that 3D-printed thymic scaffolds seeded with thymic epithelial cells and HSCs could regenerate functional thymic tissue and restore T-cell function in mice [82]. However, significant challenges remain, including the need to optimize the composition and structure of the scaffold to promote thymic regeneration and ensure its compatibility with the host immune system.

Combining stem cell-based therapies and tissue engineering approaches has emerged as a promising strategy for thymus regeneration. For example, one study showed that thymic epithelial stem cells could be seeded onto 3D-printed poly (lactic-co-glycolic acid) (PLGA) scaffolds to generate functional thymic tissue and restore T-cell function in mice [79]. Another study showed that iPSCs could be differentiated into thymic epithelial cells and seeded onto 3D-printed scaffolds to generate functional thymic tissue in vitro [83].

Gene therapy is another approach to thymus regeneration that has been explored in the literature. This approach involves the transfer of functional genes into thymic epithelial cells to correct genetic defects that may cause thymic dysfunction. For example, gene therapy has been used to correct a deficiency in FOXN1, a transcription factor essential for thymus development, in mice, resulting in the restoration of thymic function [84].

Immune modulation has also been explored as a potential approach to thymus regeneration. This approach involves the use of drugs to modulate the immune system and promote thymic regeneration. For example, interleukin-7 (IL-7), a cytokine that plays a crucial role in T-cell development, has been shown to promote thymic regeneration in animal models [78].

Small molecules are another class of compounds that have been investigated for their potential to stimulate thymus regeneration. Small molecules can be used to promote the differentiation of thymic epithelial cells and T-cell progenitors. For example, a small molecule called SR1 has been shown to promote the differentiation of functional T-cells in vitro and in vivo [84].

In conclusion, thymus regeneration, stem cells, and tissue engineering are promising approaches to address thymic involution and restore thymic function. Stem cell-based therapies, tissue engineering, and their combination have shown promise in preclinical studies for thymus regeneration. However, significant challenges remain, and further research is needed to optimize these approaches and translate them into safe and effective therapies for patients.

Conclusion

The Thymus extract therapy has emerged as a potential immunomodulatory treatment, which can be used as complementary modality in cancers and anti-aging due to its ability to stimulate T-cell production and enhance immune function. Although preliminary studies have shown promising results, further research is needed to validate its efficacy, safety, and optimal dosages. The quality and purity of thymus extract products should also be considered.

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