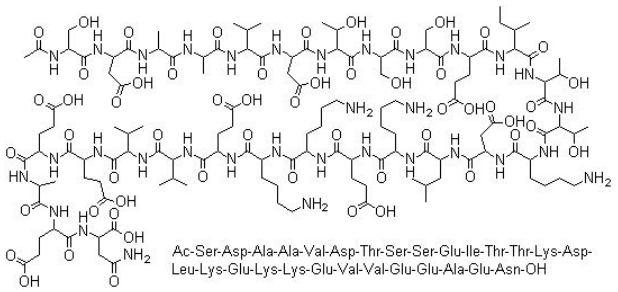
Thymosin Alpha-1

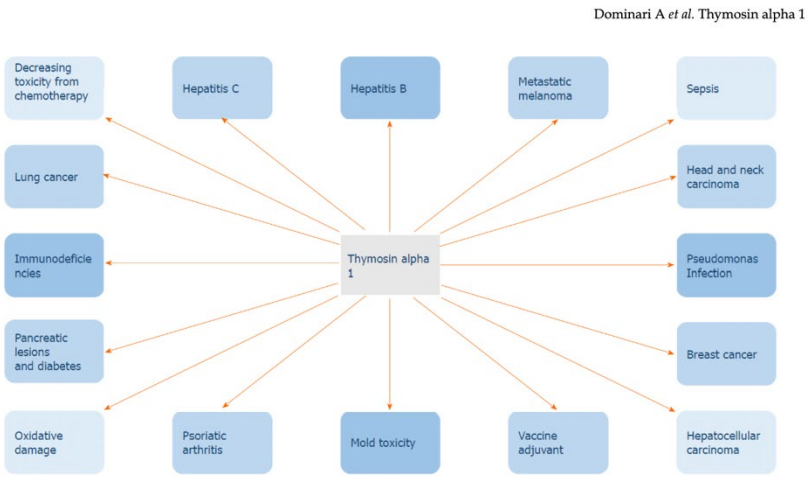
TA1
Thymalfasin
Zadaxin™

IMMUNE SUPPORTIVE PEPTIDE

Sequence: Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys- Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn-OH
Molecular Weight: 3108.28 g/mol
Molecular Formula: $C_{129}H_{215}N_{33}O_{55}$



Most Frequent Uses:
Used for clinical conditions where immune support is necessary, including:



- Hepatitis B & C
- HIV/AIDS
- Cancer – non-small cell lung (NSCLC), hepatocellular, malignant melanoma
- Chemotherapy adjunct
- Chronic inflammatory conditions; autoimmunity
- Cystic fibrosis
- Lyme disease
- Blocks steroid-induced apoptosis of thymocytes
- Depressed response to vaccinations; adjunct to flu vaccine or Geriatric immune support
- DiGeorge's syndrome
- Other conditions requiring immune response modulation

Dosage(s):
SubQ General Dosage:

- 3mg/ml 5ml vial
- 1.5 mg SubQ every 3rd day

- Treatment from 2 weeks for viral infection and 3 months or longer for HIV/ cancer / Hepatitis B, C or complicated immune suppression or over-activation
- Multiple over-lap of usage

Zadaxin™ Dosage:

- 1.6 mg, injected SubQ, 2 times weekly for 6-12 months
- Patients weighing < 40 kg, dosage adjusted to 40 mcg/kg, 2 times weekly.
- May be used together with conventional antiretroviral regimens
- Individual dosage requirements may vary based on clinical presentation

Safety and Potential Side Effects/Contraindications

- Thymosin alpha 1 peptide is reported safe in recommended dosages.
- Since 1979, thymosin alpha-1 is well tolerated. Tα1 has demonstrated a very favorable toxicity profile in more than 3,000 individuals treated to date, including patients with hepatocellular carcinoma, non–small-cell lung cancer, melanoma, and hepatitis B and C. [1,2,3,4]
- Thymosin alpha 1 has been reported to be well tolerated even in patients with decompensated liver disease, renal disease requiring hemodialysis and primary immunodeficient individuals.
- As with all injections, redness and pain at the site of injection may be present.
- Rare adverse reactions include erythema, transient muscle atrophy, polyarthralgia combined with hand edema, and rash.
- A transient increase in ALT to more than twice baseline value can occur during thymosin alpha 1 therapy. When ALT flare occurs, thymosin alpha 1 should generally be continued unless signs and symptoms of liver failure are observed.
- Use caution if administering to pregnant or nursing women.
- Do not use in individuals being deliberately immunosuppressed.
- Safety in pediatrics has not been established.

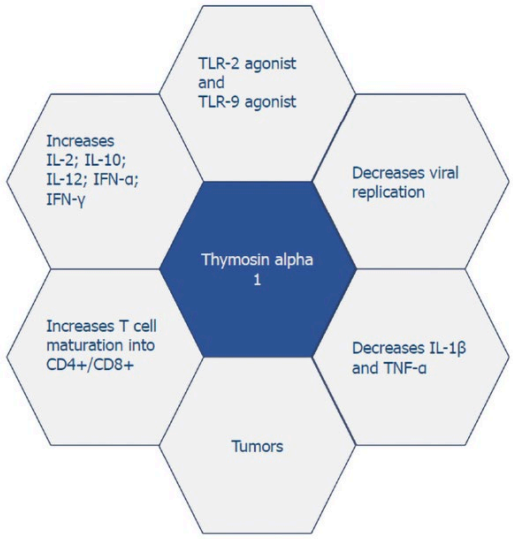
Description

Thymosin alpha-1 is a synthetic thymic peptide used to improve immune responses in times of need.[5] Studies report thymosin alpha-1: [6,7,8,9,10,11]

- Modulates innate immunity (pleiotropic)
- Improves Th1 immune responses and helps balance Th1/Th2 o Promotes T cell (Tregs) differentiation and maturation
- Decreases T-cell apoptosis
- Improves CD3+, CD4+ and CD8+
- Improves production of IL-1 beta, IFN-γ, I L-2, IL-3, IL-6, IL-10 o Improves NK cell activity and TNF-alpha
- Improves macrophages and B cells
- Up regulates MHC Class I expression in antigen expressing cell
- Tumor specific antigens; anti-tumor properties

- Inhibits viral replication
- Activates indoleamine 2,3-dioxygenase enzyme - dampens immunity
- Improves dendritic cell tryptophan catabolism
- Antioxidant properties – improves intracellular glutathione

Thymosin alpha 1 has been used to support immunity in over 3,000 patients and in over 70 clinical studies, either as monotherapy or in conjunction with current allopathic medicines.[12,13] The lack of significant side effects with thymosin alpha 1 is in sharp contrast to other major immune response modulators such as IFN and IL-2, which can lead to flu-like symptoms including malaise, fever, headache, chills and pulmonary edema (with IL-2).[14]



Thymosin alpha 1 helps the body induce effective host-derived immune effectors and balance the Th1 / Th2 arms of immunity.[15] These effector cells improve various immunomodulatory properties that lead to augmentation of T lymphocyte function, including modulation of interleukin-2 (IL-2), stimulation of interferon-g (IFN-g) production, induction of T lymphocyte and natural killer (NK) cells and stimulation of thymopoiesis. Ta1 has also been reported to up-regulate MHC Class I expression in antigen-presenting cells.[16] Additionally, Ta1 down-regulates the activity of terminal deoxynucleotide transferase (TdT) in TdT1 thymocytes, suggesting a role for Ta1 in thymocyte maturation. Ta1 has also been found to antagonize both activation induced (anti-CD3) and glucocorticoid-induced thymocyte apoptosis. It has also been reported that Ta1 stimulates activity of Indoleamine-2,3-Dioxygenase (IDO), leading to an increase in FoxP3 IL-10 producing regulatory T cells.[17] This increase leads to feedback inhibition of cytokine production, hence dampening immune response to prevent a pro-inflammatory cytokine storm and possibly autoimmune phenomena.

Immune senescence, considered an aging process, has been related to a gradual decline in thymus function and thymic hormone production.[18] The lack of thymic hormones may contribute to the decline in immune function, particularly the T cell component. In the elderly, antibody response after vaccination is compromised when compared to response in young. A similar diminished antibody response has been reported in patients with end-stage renal disease (ESRD) and in hemodialysis patients. In hemodialysis patients, this has been attributed to incompetence in T cell-mediated immune responses.

Since thymosin alpha-1 can enhance T-cell-dependent specific antibody production, Ta1 can help augment specific vaccine responses both in the elderly or in younger subjects in situations in which there are suboptimal quantities of immunizing antigen available. [19]

Efficacy of Thymosin Alpha 1 Monotherapy for Chronic Hepatitis B

Study Reference	Number of Patients Treatment Groups	Response Rate at 12-months follow up*
US Phase 2 [1,5]	12 Thymosin alpha 1 (1.6 mg SQ BIW 6 mos.) 8 Placebo	(83%) Thymosin alpha 1 (25%) Placebo
US Phase 3 [2,5]	50 Thymosin alpha 1 (1.6 mg SQ BIW 6 mos.) 49 Placebo	(24%) Thymosin alpha 1 (12%) Placebo
Taiwan Phase 3 [3,4,5]	51 Thymosin alpha 1 (1.6 mg SQ BIW 6 mos.) 53 No treatment	(37%) Thymosin alpha 1 (25%) No treatment
Pooled Data [5]	113 Thymosin alpha 1 (1.6 mg SQ BIW 6 mos.) 110 Placebo or no treatment	(36%) Thymosin alpha 1 (19%) Placebo or no treatment
*Response rate is defined as the percentage of subjects who were HBV DNA and HBeAg negative at 12-months follow up		

Efficacy of Thymosin Alpha 1 Combination Therapy with Interferon for Chronic Hepatitis C

Study Reference	Number of Patients Treatment Groups*	Response Rate at End of Treatment**	Sustained Response Rate***
US Phase 3 [6,9]	35 Thymosin alpha 1 + Interferon (Tα1 1.6 mg SQBIW 6 mos. + IFN 3 MU TIW 6 mos.)	ALT Response (37.1%) Thymosin alpha 1 + Interferon (16.2%) Interferon (2.7%) Placebo	ALT Response: (19.2%) Thymosin alpha 1 + Interferon (9.4%) Interferon
	37 Interferon (IFN 3 MU TIW 6 mos.)	Virologic Response (37.1%) Thymosin alpha 1	
	37 Placebo	+ Interferon (18.9%) Interferon (2.7%) Placebo	
Italy Phase 2 [7,9]	15 Thymosin alpha 1 (1.0 mg SQ qd for 4 days then BIW for 51 wks. + IFN 3 MU on day 4 then TIW for 51 wks.)	Virologic Response: (73.3%) Thymosin alpha 1 + Interferon	Virologic Response: (40.0%) Thymosin alpha 1 + Interferon
Italy Phase 2 [8,9]	17 Thymosin alpha 1 (1.6 mg SQ BIW for 6 mos. + +IFN 3 MU TIW 6 mos.) 17 Interferon	ALT Response: (70.6%) Thymosin alpha 1 + Interferon (35.3%) Interferon	ALT Response: (29.4%) Thymosin alpha 1 + Interferon (17.6%) Interferon
Pooled Data [9]	67 Thymosin alpha 1 (1.6 mg SQ BIW 6 to 12 mos. IFN 3 MU TIW 6 to 12 mos.) 54 Interferon	ALT Response: (44.7%) Thymosin alpha 1 + Interferon (22.2%) Interferon+	ALT Response: (22.4%) Thymosin alpha 1 + interferon (9.3%) Interferon**

*Intent-to-treat analysis
**ALT Response Rate is defined as the percentage of subjects who had normal ALT at end of treatment. Virologic Response Rate is defined as the percentage of subjects who were HCV RNA negative at end of treatment.
*** ALT Response Rate is defined as the percentage of subjects who had normal ALT at end of 6 months follow up Virologic Response Rate is defined as the percentage of subjects who were HCV RNA negative at end of 6 months follow up. US Phase 3 sustained response includes patients treated for 6 months and relapsers retreated for a total of 12 months.
+P=0.0096
++P=0.10

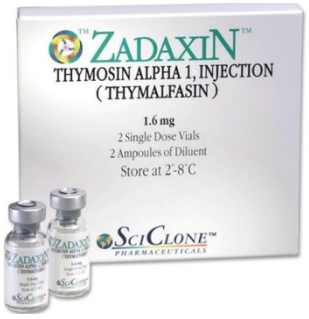
Efficacy of Thymosin Alpha 1 as Adjuvant Therapy for Some Types of Cancer

Study Reference	Number of Patients Treatment Groups	Clinical Outcome
Italy pilot study (HCC) [10]	12 Thymosin alpha 1 (1.6 mg SQ BIW 6 mos.)+TACE 12 TACE only	Statistically significant survival benefit and mprovement in immunological parameters in thymosin alpha 1 treated group compared with historical controls
US Phase 3 (NSCLC primarily Stage III) [11]	28 Thymosin alpha 1, 0.9 mg/m^2 SQ BIW up to 12 mos 13 placebo Thymosin alpha 1 treatment followed radiation therapy	Recurrence-free survival (p = 0.04) Greater effect in nonbulky vs. bulky tumors, p = 0.01 Median survival 52$^+$ vs. 32 wks Overall survival: p = 0.002
Italy Phase 2 (NSCLC, Stage II & IV) [12]	12 thymosin alpha 1, 1 mg SQ on days 8 to 11 and 15 to 18 + Ifosfamide + IFN-α3 MIU on days 11 and 18 10 Ifosfamide	Objective response: 66% vs. 10% Median time to progression: 18 wks vs. 9 wks (p = 0.0059) Median survival duration: 24 wks vs. 16 wks > 1 yr survival: 3 (35%) vs. 2 (20%) Lymphocyte count: maintained vs. decreased Hematologic toxicity reduced with no grade 3/4 toxicity compared to 50% in chemotherapy group
Italy Phase 2 (Malignant Melanoma) [13]	27 Thymosin alpha 1, 1 mg SQ on days 8 to 11 and 15 to 18 + DTIC + IFN-α Cycle repeated every 4 wks for 6 times (6 mos) or until disease progression	Overall response rate: 45% mean response duration: 13.5 mos
Italy Phase 2 (Malignant Melanoma) [14]	46 Thymosin alpha 2, mg s.c days 4-7 + DTIC + IL-2 Cycle repeated every 3 wks up to 6 times (app. 4 mos) Follow- up to 29 mos	Overall response rate: 36% Median time to progression: 5.5 mos Median survival: 11 mos (48% survived greater than 1 yr)

- Charts from Zydaxin product literature.

Zadaxin™

Zadaxin (Thymalfasin, SciClone Pharmaceuticals, China) is a thymosin alpha-1 peptide that has been evaluated for its immunomodulatory activities and related therapeutic potential in several diseases, including chronic hepatitis B and C, acquired immunodeficiency syndrome (AIDS), primary immunodeficiency diseases, depressed response to vaccination, and cancer.[20] Zadaxin is currently in Phase III trials for the treatment of hepatitis C and in Phase II trials for hepatitis B in the US.



Clinical Research

IPS Level of Evidence

IPS Clinical Pharmacists have developed a method of ranking the studies so that the practitioner can easily discern the level of evidence this study provides to the topic. Levels 1-8 are listed below:

	Level of Evidence	Description
	Level 1	FDA Approved Drug studies
X	Level 2	Evidence obtained from systematic review and/or meta-analyses of studies including RCTs and other human studies
X	Level 3	Evidence obtained from a RCT
X	Level 4	Evidence obtained from a study without randomization
	Level 5	Evidence obtained from case reports
X	Level 6	Evidence obtained from *in vitro* human studies
X	Level 7	Evidence obtained from laboratory animal studies
X	Level 8	Evidence obtained from Opinions or Reviews

Table 1 Summarizing pre-clinical and clinical studies

Pre-clinical studies		
Ref.	**Year**	**Application of thymosin alpha 1**
Guo *et al*[36]	2015	The anti-tumor effect of thymosin alpha 1 was studied on human cancer cell lines. The study concluded that thymosin alpha 1 can decrease proliferation and induce apoptosis in human leukemia, non-small cell lung cancer, melanoma, and other cancers. The study concluded that thymosin alpha 1 could be an approach to breast cancer treatment
Clinical studies		
Sherman *et al*[29]	2010	Thymosin alpha 1 was tested as monotherapy and in combination with interferon-alpha for the treatment of chronic hepatitis B. It was also shown to stimulate IL-2 receptor expression and IL-2 internalization and to enhance immune response in patients with immunodeficiency
Eckert *et al*[30]	1994	Combination therapy of thymosin alpha 1 and pegylated interferon alpha 2a preferred over interferon monotherapy for the treatment of chronic hepatitis C
Li *et al*[8]	2015	Significant decrease in mortality due to multiple organ failure in patients with sepsis
Li *et al*[6]	2010	Thymosin alpha 1 can be safely used as an adjuvant to antiretroviral therapy in HIV patients. It helps increase CD4+ count, stimulates the function of CD4+ cells, and helps decrease viral load. By amplifying the activity of catalase, superoxide dismutase, and glutathione peroxidase, it decreases oxidative damage to tissues. Thymosin alpha 1 reduces tumor cell proliferation in human malignancies by decreasing oxidative stress
Matteucci *et al*[2]	2017	Thymosin alpha 1 significantly increases levels of sjTREC in patients with advanced HIV disease
Camerini *et al*[1]	2015	Thymosin alpha 1 can be used in pseudomonas infections or infections following bone marrow transplant
Antachopoulos *et al*[7]	2012	Thymosin alpha 1 might be effective against mold toxicity
King *et al*[13]	2016	Thymosin alpha 1 increases cytokine production and is expected to be beneficial in immunocompromised patients
Pica *et al*[4]	2018	It has been postulated that thymosin alpha 1 can help regulate immunity and reduce inflammation in patients with psoriatic arthritis
Panatto *et al*[31]	2011	Thymosin alpha 1 has shown promising results as an adjuvant to the influenza vaccine
Carraro *et al*[3]	2012	Thymosin alpha 1 improves immunogenicity of the influenza vaccine
Qin *et al*[32]	2009	Thymosin alpha 1 can reduce oxidative damage to the pancreas and mitigate the risk of resulting diabetes
Costantini *et al*[33]	2019	Thymosin alpha 1 has shown promising results in patients with malignancies, such as metastatic melanoma, head and neck carcinoma, lung cancer, breast cancer, and hepatocellular carcinoma
Romani *et al*[21]	2007	A single-blind randomized control trial was conducted in six tertiary hospitals in China to study the beneficial effects of thymosin alpha 1 on patients with sepsis. The results showed 9% lower mortality in the treatment group compared to the control group
Sugahara *et al*[37]	2002	Patients with chronic hepatitis B who were treated with thymosin alpha 1 showed an overall improvement in serum ALT levels. ALT levels were reduced to normal in 42.9%. A total disappearance of serum HBV DNA was noted in 28.6% of patients

Liu Y, et al. **Thymosin alpha 1 (Tα1) reduces the mortality of severe COVID-19 by restoration of lymphocytopenia and reversion of exhausted T cells.**

LEVEL 2

Abstract: Background: Thymosin alpha 1 (Tα1) had been used in the treatment of viral infections as an immune response modifier for many years. However, clinical benefits and the mechanism of Tα1 treatment for COVID-19 patients are still unclear.
Methods: We retrospectively reviewed the clinical outcomes of 76 severe COVID-19 cases admitted to 2 hospitals in Wuhan, China, from December 2019 to March 2020. The thymus output in peripheral blood mononuclear cells from COVID-19 patients was measured by T-cell receptor excision circles (TRECs). The levels of T-cell exhaustion markers programmed death-1 (PD-1) and T-cell immunoglobulin and mucin domain protein 3 (Tim-3) on CD8+ T cells were detected by flow cytometry.
Results: Compared with the untreated group, Tα1 treatment significantly reduced the mortality of severe COVID-19 patients (11.11% vs 30.00%, P = .044). Tα1 enhanced blood T-cell numbers in COVID-19 patients with severe lymphocytopenia. Under such conditions, Tα1 also successfully restored CD8+ and CD4+ T-cell numbers in elderly patients. Meanwhile, Tα1 reduced PD-1 and Tim-3 expression on CD8+ T cells from severe COVID-19 patients compared

with untreated cases. It is of note that restoration of lymphocytopenia and acute exhaustion of T cells were roughly parallel to the rise of TRECs. **Conclusions:** Tα1 treatment significantly reduced mortality of severe COVID-19 patients. COVID-19 patients with counts of CD8+ T cells or CD4+ T cells in circulation less than 400/μL or 650/μL, respectively, gained more benefits from Tα1. Tα1 reversed T-cell exhaustion and recovered immune reconstitution through promoting thymus output during severe acute respiratory syndrome-coronavirus 2 infection.

https://www.semanticscholar.org/paper/Thymosin-alpha-1-(T%CE%B11)-reduces-the-mortality-of-by-Liu-Pan/d2cda3c6b99b5314e0ae982a54c23b9d300bfb05

Sherman KE. **Thymosin alpha 1 for treatment of hepatitis C virus: promise and proof**. Ann N Y Acad Sci. 2010;1194:136–140.

LEVEL 2

Abstract: The hepatitis C virus (HCV) is a global public health problem, with chronic infection leading to development of cirrhosis, end-stage liver disease and hepatocellular carcinoma (HCC). Treatment of HCV is suboptimal with overall response rates of slightly greater than 50% when patients are treated with pegylated interferon alfa and ribavirin. Thymosin alpha 1 (Talpha1; TA-1) is an immunomodulatory peptide with intrinsic activities that might improve treatment outcomes for HCV by incorporation of this agent in current treatment paradigms. An extensive body of literature supports a possible role for this agent in difficult to treat populations. However, clinical trials to date have failed to conclusively support the role of TA-1 in combination interferon-based therapies. Therefore, the promise of TA-1 adjunctive therapy for HCV remains, but the proof will require investment in large randomized clinical trials of appropriate patient populations.

Full Text Not Available

Carraro G, et al. **Thymosin-alpha 1 (Zadaxin) enhances the immunogenicity of an adjuvated pandemic H1N1v influenza vaccine (Focetria) in hemodialyzed patients: a pilot study**. Vaccine. 2012;30(6):1170-80.

LEVEL 3

Abstract: Background: Although influenza vaccination is widely recommended for immunosuppressed people, the same immune dysfunction that can increase the risk of contracting influenza might also compromise vaccine effectiveness, especially during

pandemics. Clinical data have highlighted the role of adjuvants in improving vaccine efficacy. As uremic patients are especially vulnerable to infections, it is recommended that they should be vaccinated yearly against influenza. This paper presents the results of a pilot clinical trial, conducted in hemodialyzed patients with an adjuvated pandemic H1N1v influenza vaccine alone and combined with Thymosin-alpha 1. **Methods:** Subjects were subdivided into 3 treatment groups receiving: the adjuvated pandemic influenza vaccine (Focetria) only (first treatment group), and the Vaccine+Thymosin alpha 1 (Zadaxin) at a dose of 3.2 and 6.4 mg (second and third treatment groups respectively). The immunoresponse was assessed on days 0, 21, 42, 84 and 168 after vaccine administration by means of Hemagglutination Inhibition (HI), Microneutralization (MN) and Single Radial Hemolysis (SRH) assays. The CHMP regards HI as the gold standard test to evaluate the immune response to influenza vaccines before influenza vaccines are licensed. The CHMP criteria are slightly different in adults (18-60-year-old subjects) and the elderly (>60 years old). Indeed, 40% of seroconversion, 70% of subjects seroprotected 21 days after vaccination, and a 2.5-fold increase in GMR (Geometric Mean Ratio) are required in adults, while in the elderly, the corresponding threshold values are: 30%, 60% and a 2-fold increase. All these criteria must be met for the licensing of a pandemic influenza vaccine. Safety evaluation was performed by means of Adverse Event (AE) recording, laboratory assays (hematology and chemistry), electrocardiogram, and assessment of vital signs. **Results:** Three populations were considered: Intention-To-Treat (ITT) (94 patients), Per Protocol (PP) (82 patients), and Safety population (99 patients). With regard to the Geometric Mean Titer (GMT) and the Geometric Mean Ratio (GMR) of HI on Day 21 in the ITT population, both "Vaccine+Thymosin alpha 1" groups presented better results than the "Vaccine only" group. A large proportion of ITT patients in the two Vaccine+Thymosin alpha 1 groups achieved seroconversion by Day 21. On Day 42, the decrease in the GMT of HI was greater in the Vaccine+Thymosin alpha 1 groups than in the vaccine only group. Similar results were obtained in the PP population. The CHMP criteria were fully met in the groups treated with Vaccine+Thymosin alpha 1. No AE was found to be related to Thymosin alpha 1 nor to the Focetria vaccine. **Conclusions:** Although further studies in larger hemodialyzed populations are necessary, it can be concluded that Thymosin alpha 1 enhanced the immunogenicity of the pandemic influenza vaccine used. Moreover, it proved safe and well tolerated, and did not affect hematology or blood-chemistry values.

https://sci-hub.se/10.1016/j.vaccine.2011.12.014

Gravenstein S, et al. **Augmentation of influenza antibody response in elderly men by thymosin alpha one. A double-blind placebo-controlled clinical study**. J Am Geriatr Soc. 1989;37(1):1-8.

LEVEL 3

Abstract: Influenza remains a major cause of illness and death in elderly people despite current vaccination programs. One factor is an immunization failure rate in the elderly that may be as high as 50%. To test whether administration of thymosin alpha 1 would result in greater antibody production, we administered it (900 micrograms/m2 subcutaneously twice weekly for eight

doses) in conjunction with the 1986 trivalent influenza vaccine. Ninety men (65-99 years old, mean age 77.3 years) were randomized double-blind to receive thymosin alpha 1 or placebo by the same schedule; the sera from 85 of these men were acceptable for analysis. The two groups were similar with respect to underlying disease, medications, and age. No toxicity was observed in either group. Antibody response rate was defined as a four-fold rise in antibody titer over 3-6 weeks following vaccination and was measured by an enzyme-linked immunosorbent assay (ELISA). Analysis was performed on treatment groups and subgroups divided by the mean age: the older group consisted of subjects aged 77 years and older, and the younger group those aged from 65-76 years. Baseline and change in absolute antibody levels were compared by t test and using age as a continuous variable by multiple regression analysis.

No Full Text Available

Qui S, et al. **A multicenter, randomized, observation-controlled clinical trial to evaluate the efficacy and safety of thymalfasin adjuvant therapy in patients with HBV-related HCC after curative resection - first announcement of the protocol**. Exp Opin Biol Therapy. 2015;15(Suppl 1):5133-37.

Abstract: Hepatocellular carcinoma (HCC), the third leading cause of cancer-related death worldwide, is a disease of immune microenvironment. Chronic Hepatitis B virus (HBV) infection, also an immune-related disease, is the major etiological factor for HCC especially in Asia. As an immune regulator, which has pleiotropic activities on T cells, nature killer cells and dendritic cells and so on, the efficacy of thymalfasin on HCC patients has been proven by several pilot studies as an adjuvant therapy. Combination of thymalfasin significantly improved survival and prolonged the time to tumor recurrence in patients who received transcatheter arterial chemoembolization after tumor resection. An improvement in patients' immunity has also been demonstrated. However, there is no large-scale randomized controlled study so far in resectable HCC patients. To confirm the role of thymalfasin adjuvant therapy in patients with HBV-related HCC after curative resection, a large-scale multicenter randomized controlled trial has been planned in China to investigate the effect of thymalfasin (1.6 mg twice a week for 12 months) on 2-year recurrence-free survival rate and tumor immune microenvironment. Here is the first announcement of the study protocol (ClinialTrials.gov Identifier: NCT02281266).

https://sci-hub.se/10.1517/14712598.2015.1039979

Wang Z, et al. **Thymosin Alpha-1 Has no Beneficial Effect on Restoring CD4+ and CD8+ T Lymphocyte Counts in COVID-19 Patients**. Front Immunol. 2021;12:568789.

Abstract: Dysregulation of immune response was observed in COVID-19 patients. Thymosin alpha 1 (Tα1) is used in the management of COVID-19, because it is known to restore the homeostasis of the immune system during infections and cancers. We aim to observe the longitudinal changes in T lymphocyte subsets and to evaluate the efficacy of Tα1 for COVID-19. A retrospective study was conducted in 275 COVID-19 patients admitted to Shanghai public health clinical center. The clinical and laboratory characteristics between patients with different T lymphocyte phenotypes and those who were and were not treated with Tα1 were compared. Among the 275 patients, 137 (49.8%) were males, and the median age was 51 years [interquartile range (IQR): 37-64]. A total of 126 patients received Tα1 therapy and 149 patients did not. There were 158 (57.5%) patients with normal baseline CD4 counts (median:631/μL, IQR: 501~762) and 117 patients (42.5%) with decreased baseline CD4 counts (median:271/μL, IQR: 201~335). In those with decreased baseline CD4 counts, more patients were older ($p<0.001$), presented as critically ill ($p=0.032$) and had hypertension ($p=0.008$) compared with those with normal CD4 counts. There was no statistical difference in the duration of virus shedding in the upper respiratory tract between the two groups ($p=0.214$). In both the normal (14 *vs* 11, $p=0.028$) and the decreased baseline CD4 counts group (15 *vs* 11, $p=0.008$), duration of virus clearance in the patients with Tα1 therapy was significantly longer than that in those without Tα1 therapy. There was no significant difference in the increase of CD4+ (286 *vs* 326, $p=0.851$) and CD8+ T cell (154 *vs* 170, $p=0.842$) counts in the recovery period between the two groups with or without Tα1 therapy. Multivariate linear regression analysis showed that severity of illness ($p<0.001$) and Tα1 therapy ($p=0.001$) were associated with virus clearance. In conclusion, reduction of CD4+ T and CD8+ T cell counts were observed in COVID-19 patients. Tα1 may have no benefit on restoring CD4+ and CD8+ T cell counts or on the virus clearance. The use of Tα1 for COVID-19 need to be more fully investigated.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8209490/pdf/fimmu-12-568789.pdf

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Li X, et al. **Gender-associated difference following COVID-19 virus infection: Implications for thymosin alpha-1 therapy**. Int Immunopharmacol. 2021;90:107022.

LEVEL 4

Abstract: Gender influences clinical presentations, duration and severity of symptoms, and therapy outcome in coronavirus disease 2019 (COVID-19) infection. Whether the immune response to Tα1 treatment for SARS-CoV-2 differs between the sexes, and whether this difference explains the male susceptibility to COVID-19, is unclear. This study aimed to investigate the efficiency and safety of Tα1 treatment and provide a basis for practically identifying gender differences characteristics and features of COVID-19. One hundred twenty-seven patients had COVID-19 symptoms and tested COVID19-positive (female 42.52%) in Wuhan union hospital were enrolled for medication. They were randomly divided into groups Control and Tα1 intervention. Seventy-eight patients received a subcutaneous injection of 1.6 mg Tα1, based on supportive treatment for 15 days. The control group included untreated 49 COVID19 patients closely matched for gender and age and received regular supportive treatment. In this retrospective analysis, we found that COVID-19-infected males reported more

symptoms than COVID-19-infected females. A high degree of gender differences-related variability was observed in CRP and PCT levels and the cell counts of many lymphocyte subpopulations in the COVID-19 patients after Tα1 intervention. Levels of CRP and IL-6 were higher in Tα1-treated male group than Tα1-treated female group, while the level of PCT was significantly lower in Tα1-treated male group. Gender differences may be a factor in sustaining COVID-19 immunity responded to Tα1, male and female show statistically significant differences in relevance to cytokine production associated with the development of a more significant number of symptoms. This leaves the question of identifying gender-specific risk factors to explain these differences.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7500882/pdf/main.pdf

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He C, et al. **Thymalfasin, a promising adjuvant therapy in small hepatocellular carcinoma after liver resection.** Medicine. 2017;96(16):e6606.

Abstract: There is limited information available concerning the effect of thymalfasin (Tα1) as an adjuvant therapy in hepatocellular carcinoma (HCC) patient who received liver resection. The present study aimed to evaluate whether Tα1 can improve the prognosis of small HCC patients after liver resection.A total of 206 patients with small HCC who underwent liver resection were analyzed in our retrospective cohort study. Patients were divided into 2 groups: group A (resection+Tα1, n=44) and group B (resection, n=162). Clinical data, overall survival (OS), and recurrence-free survival (RFS) were compared. Prognostic factors were identified using multivariate analysis.After a median follow-up of 47.0 months, 134 patients (65%) had recurrence, and 62 patients (30.09%) died. The 1, 3, and 5-year OS rate of patients in group A was 97.7%, 90.6%, and 82.9%, respectively, and 95.1%, 80.5%, and 62.9%, respectively, for patients in group B (P=.014). The 1, 3, and 5-year RFS rate of patients in group A was 70.5%, 56.8%, and 53.3%, respectively, and 65.8%, 41.3%, and 32.1%, respectively, for patients in group B (P=.015). Multivariate analysis indicated that Tα1 was an independent prognostic factor for both OS (P=.015, hazard ratio 0.349, 95% confidence interval 0.149-0.816) and RFS (P=.019, hazard ratio 0.564, 95% confidence interval 0.349-0.910).Tα1 as an adjuvant therapy after liver resection may improve the prognosis of small HCC patients after liver resection.

https://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC5406071&blobtype=pdf

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Stefanini GF, et al. **Alpha-1-thymosin and transcatheter arterial chemoembolization in hepatocellular carcinoma patients: A preliminary experience.** Hepatogastroenterology 45: 209– 215,1998

Abstract:Background/aims: To evaluate the tolerability and therapeutic potential of the immunostimulating adjuvant alpha-1-thymosin in patients with hepatocellular carcinoma. **Methodology:** Twelve patients with hepatocellular carcinoma were treated with alpha-1-thymosin (900 micrograms/m2 subcutaneously twice per week for 6 months) and transcatheter arterial chemoembolization and compared to a historical control group (matched for gender, age, Okuda staging, Child's score, alpha-fetoprotein serum levels and viral infection) treated with transcatheter arterial chemoembolization alone. **Results:** No severe side effects were recorded in the 2 treatment groups. The combination of alpha-1-thymosin plus transcatheter arterial chemoembolization resulted in a longer survival that reached statistical significance 7 months after the end of treatment ($p < 0.05$). Patients receiving combined treatment demonstrated a significant increase in peripheral blood mononuclear cells expressing CD3 ($p < 0.05$) and CD8 ($p < 0.025$) 3 months after beginning treatment. They also had a significant increase ($p < 0.05$) in CD16+ and CD56+ cells after 1 month, and a slight reduction in mononuclear cells expressing CD25, a marker for cell activation. No alterations in the response to phytohemagglutinin stimulation were seen during the alpha-1-thymosin treatment. **Conclusions:** The absence of toxicity and the favourable effects observed in this open study call for a double blind control study to confirm the efficacy of the combined treatment.

No Full Text Available

Linye H, et al. **Thymosin alpha-1 therapy improves postoperative survival after curative resection for solitary hepatitis B virus-related hepatocellular carcinoma.** Medicine. 2021;100(20):e25749.

Abstract: Thymosin alpha-1 (Tα1) is an immunomodulatory and antiviral agent with potential effects on chronic hepatitis B and liver cancer. Its impact on solitary hepatocellular carcinoma (HCC) remains controversial, so we aimed to investigate the efficacy of Tα1 in solitary HBV-related HCC patients after curative resection. Between May 2010 and April 2016, 468 patients with solitary HBV-related HCC after curative resection were analyzed. Propensity score matching (PSM) was used to minimize confounding variables. Risk factors were identified by the Cox proportional hazards model. Recurrence-free survival (RFS) rates, overall survival (OS) rates, immunological, and virologic response were compared. The median follow up was 60.0 months. Immunological response improved in the Tα1 group compared with the control group ($P < .001$) but the virologic response was similar between 2 groups after 24 months. Patients with Tα1 therapy had better RFS and OS before ($P = .018$ and $P < .001$) and after ($P = .006$ and $P < .001$) propensity matching. Multivariate analysis revealed that Tα1 therapy was an independent prognostic factor for both OS ($P < .001$, HR = 0.308, 95% CI: 0.175–0.541) and

RFS ($P < .001$, HR = 0.381, 95% CI: 0.229–0.633). Tα1 as an adjuvant therapy improves the prognosis of solitary HBV-related HCC patients after curative liver resection.

https://journals.lww.com/md-journal/Fulltext/2021/05210/Thymosin_alpha_1_therapy_improves_postoperative.15.aspx

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Qin Y, et al. **Proliferative and anti-proliferative effects of thymosin α1 on cells are associated with manipulation of cellular ROS levels**. Chem Biol Interact. 2009;180(3):383-8.

LEVEL 6

Abstract: Reactive oxygen species (ROS) are constantly generated and eliminated in the biological system and play important roles in a variety of physiological and pathological processes. Previous studies indicate that modulation of cellular ROS affects cell proliferation. Thymosin alpha 1 (Talpha1) is a naturally occurring thymic peptide and has previously been shown to be a potential therapy for some immunodeficiencies, malignancies, and infections. However, few reports have focused on manipulation of cellular ROS level effects of Talpha1. In this study, the Talpha1-treated leukomonocytes, which were isolated from mice spleens, exhibited a higher ROS level and a lower reduced glutathione (GSH) level; however, HepG2 cells treated with Talpha1 exhibited lower ROS level and higher GSH level. In addition, after treatment with Talpha1, the population of leukomonocytes in the G(2) phase increased, resulting in a slight increase in viability. However, in Talpha1-treated HepG2 cells, the cell cycle was delayed in the G(1) phase, thereby inhibiting tumor cell proliferation; in addition, dephosphorylation of the serine/threonine kinase Akt was detected. In conclusion, we show that Talpha1 has potent anti-proliferative activity against malignant human hepatoma cells and proliferative activity against leukomonocytes associated with manipulation of oxidative stress levels which indicates the potential of Talpha1 as an antitumor drug.

https://www.researchgate.net/publication/24427734_Proliferative_and_anti-proliferative_effects_of_thymosin_a1_on_cells_are_associated_with_manipulation_of_cellular_ROS_levels

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Garaci E, et al. **Thymosin α1 and cancer: action on immune effector and tumor target cells**. Ann N Y Acad Sci. 2012;1269:26-33.

LEVEL 6

Abstract: Since it was first identified, thymosin alpha 1 (Tα1) has been characterized to have pleiotropic effects on several pathological conditions, in particular as a modulator of immune

response and inflammation. Several properties exerted by Tα1 may be attributable to a direct action on lymphoid cells. Tα1 has been shown to exert an immune modulatory activity on both T cell and natural killer cell maturation and to have an effect on functions of mature lymphocytes, including stimulating cytokine production and cytotoxic T lymphocyte-mediated cytotoxic responses. In previous studies we have shown that Tα1 increases the expression of major histocompatibility complex class I surface molecules in murine and human tumor cell lines and in primary cultures of human macrophages. In the present paper, we describe preliminary data indicating that Tα1 is also capable of increasing the expression of tumor antigens in both experimental and human tumor cell lines. This effect, which is exerted at the level of the target tumor cells, represents an additional factor increasing the antitumor activity of Tα1.

https://sci-hub.se/10.1111/j.1749-6632.2012.06697.x

Huang Y, et al. **The modulation of thymosin alpha 1 in the maturation, differentiation and function of murine bone marrow-derived dendritic cells in the absence or presence of tumor necrosis factor-alpha**. Int Immunopharmacol. 2004;4(4):539-46.

LEVEL 6

Abstract: Thymosin alpha 1 (Talpha1) has immunomodulatory effects on T-cells, NK-cells and macrophages, but its action on dendritic cells (DCs), which are recognized as the sole professional antigen presenting cells (APCs) capable of priming naïve T-cells, is poorly understood. In this study, the effect of Talpha1 in vitro on murine bone marrow-derived DCs (BMDCs) maturation, differentiation, and function with or without tumor necrosis factor-alpha (TNF-alpha), which is one of the important inflammatory parameters, has been investigated. We have shown, through flow cytometry, ELISA and mixed leukocyte reaction (MLR), that Talpha1 promoted CD4-expressed DC differentiation and the expression of activation markers, but did not influence IL-12 production and T cell-stimulatory capacity of DCs in the absence of TNFalpha during BMDCs maturation. Furthermore, in the presence of TNF-alpha, Talpha1 has been shown not only to promote the expression of CD4 on MHC class II+ DCs and enhance the up-regulated levels of mature markers induced by TNF-alpha, but also to suppress the up-regulated IL-12 production. Particularly, thus effects seen were obvious at pharmacological Talpha1 concentrations. However, Talpha1 did not inhibit TNF-alpha-induced T-cell stimulating function of DCs. This is the first reported example of a direct Talpha1-DC interaction and suggests a mechanism by which Talpha1 may in part affect T-cell responses by acting at the DC level and it may play an important role in the modulation of the local inflammatory responses in vivo.

https://sci-hub.se/10.1016/j.intimp.2004.02.008

Guo Y, et al. **Thymosin alpha 1 suppresses proliferation and induces apoptosis in breast cancer cells through PTEN-mediated inhibition of PI3K/Akt/mTOR signaling pathway**. Apoptosis. 2015;20(8):1109-21.

LEVEL 6

Abstract: Thymosin alpha 1 (Tα1), an immunoactive peptide, has been shown to inhibit cell proliferation and induce apoptosis in human leukemia, non-small cell lung cancer, melanoma, and other human cancers. However, the response and molecular mechanism of breast cancer cells exposed to Tα1 remain unclear. PTEN, a tumor suppressor gene, is frequently mutated in a variety of human cancers. In the present study, we aimed to investigate the biological roles of PTEN in the growth inhibition of human breast cancer cells exposed to Tα1. Using wild-type and mutant PTEN-expressing cells, we found a strong correlation between PTEN status and Tα1-mediated growth inhibition of breast cancer cells. The growth inhibition effect was more pronounced in breast cancer cells in which Tα1 enhanced PTEN expression, whereas endogenous PTEN knockdown reversed the growth inhibition effect of Tα1 in breast cancer cells. Further investigation revealed that PTEN up-regulation, which was induced by Tα1, can inhibit the activation of the PI3K/Akt/mTOR signaling pathway, leading to the growth inhibition of breast cancer cells. The addition of the synergy between Tα1 and the inhibition of PI3K/Akt/mTOR activation could strongly block cell viability in PTEN down-regulated breast cancer cells. PTEN-overexpressing cells not only up-regulated Bax and cleaved caspase-3/9 and PARP expression but also down-regulated Bcl-2 compared to the treatment with Tα1 alone. Together these findings suggest that PTEN mediates Tα1-induced apoptosis through the mitochondrial death cascade and inhibition of the PI3K/Akt/mTOR signaling pathway in breast cancer cells.

https://sci-hub.se/10.1007/s10495-015-1138-9

Dominari A, et al. **Thymosin alpha 1: a comprehensive review of the literature**. World J Virol. 2020;9(5):67-78.

LEVEL 8

ABSTRACT: Thymosin alpha 1 is a peptide naturally occurring in the thymus that has long been recognized for modifying, enhancing, and restoring immune function. Thymosin alpha 1 has been utilized in the treatment of immunocompromised states and malignancies, as an enhancer of vaccine response, and as a means of curbing morbidity and mortality in sepsis and numerous infections. Studies have postulated that thymosin alpha 1 could help improve the outcome in severely ill corona virus disease 2019 patients by repairing damage caused by overactivation of lymphocytic immunity and how thymosin alpha 1 could prevent the excessive activation of T cells. In this review, we discuss key literature on the background knowledge and current clinical uses of thymosin alpha 1. Considering the known biochemical properties

including antibacterial and antiviral properties, time-honored applications, and the new promising findings regarding the use of thymosin, we believe that thymosin alpha 1 deserves further investigation into its antiviral properties and possible repurposing as a treatment against severe acute respiratory syndrome coronavirus-2.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7747025/pdf/WJV-9-67.pdf

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Costantini C, et al. **A reappraisal of thymosin alpha 1 in cancer therapy**. Front Oncol. 2019;9:873.

LEVEL 8

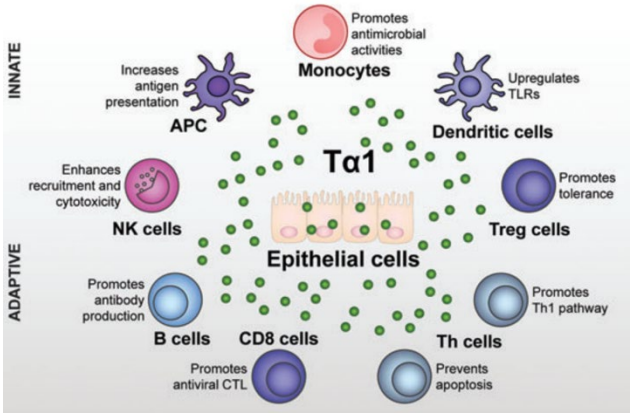
Abstract: Thymosin alpha1 (Tα1), an endogenous peptide first isolated from the thymic tissue in the mid-sixties, has gained considerable attention for its immunostimulatory activity that led to its application to diverse pathological conditions, including cancer. Studies in animal models and human patients have shown promising results in different types of malignancies, especially when Tα1 was used in combination with other chemo- and immune therapies. For this reason, the advancements in our knowledge on the adjuvant role of Tα1 have moved in parallel with the development of novel cancer therapies in a way that Tα1 was integrated to changing paradigms and protocols, and tested for increased efficacy and safety. Cancer immunotherapy has recently experienced a tremendous boost following the development and clinical application of immune checkpoint inhibitors. By unleashing the full potential of the adaptive immune response, checkpoint inhibitors were expected to be very effective against tumors, but it soon became clear that a widespread and successful application was not straightforward and shortcomings in efficacy and safety clearly emerged. This scenario led to the development of novel concepts in immunotherapy and the design of combination protocols to overcome these limitations, thus opening up novel opportunities for Tα1 application. Herein, we summarize in a historical perspective the use of Tα1 in cancer, with particular reference to melanoma, hepatocellular carcinoma and lung cancer. We will discuss the current limitations of checkpoint inhibitors in clinical practice and the mechanisms at the basis of a potential application of Tα1 in combination protocols.

https://sci-hub.se/10.3389/fonc.2019.00873

Romani L, et al. **Jack of all trades: thymosin alpha 1 and its pleiotropy**. Ann N Y Acad Sci. 2012;1269:1-6.

LEVEL 8

Abstract: Thymosin 1 (T1), a thymosin-related 28-mer synthetic amino-terminal acetylated peptide, has gained increasing interest in recent years, due to its pleiotropy. The peptide has been used worldwide as an adjuvant or immunotherapeutic agent to treat disparate human diseases, including viral infections, immunodeficiencies, and malignancies. The peptide can enhance T cell, dendritic cell (DC), and antibody responses, modulate cytokine and chemokine production, and block steroid-induced apoptosis of thymocytes. Its central role in modulating DC function and activating multiple signaling pathways that contribute to different functions may offer a plausible explanation for its pleiotropic action. Additionally, the ability of T1 to activate the indoleamine 2,3-dioxygenase enzyme—which confers immune tolerance during transplantation and restrains the vicious circle of chronic inflammation—has been a turning point, suggesting a potential, specific function in immunity. Accordingly, T1 has recently been shown to promote immune reconstitution and improve survival of recipients of HLA-matched sibling T cell–depleted stem cell transplants in a phase I/II clinical trial. Thus, T1 continues to live up to its promises.



https://sci-hub.se/10.1111/j.1749-6632.2012.06716.x

Romani L, et al. **Thymosin alpha 1: an endogenous regulator of inflammation, immunity and tolerance.** Ann N Y Acad Sci. 2007;1112:236-38.

LEVEL 8

Abstract: Thymosin alpha1 (Talpha1), first described and characterized by Allan Goldstein in 1972, is used worldwide for the treatment of some immunodeficiencies, malignancies, and infections. Although Talpha1 has shown a variety of effects on cells and pathways of the immune system, its central role in modulating dendritic cell (DC) function has only recently been appreciated. As DCs have the ability to sense infection and tissue stress and to translate collectively this information into an appropriate immune response, an action on DCs would predict a central role for Talpha1 in inducing different forms of immunity and tolerance. Recent results have shown that Talpha1: (a) primed DCs for antifungal Th1 resistance through Toll-like receptor (TLR)/MyD88-dependent signaling and this translated in vivo in protection against aspergillosis; (b) activated plasmacytoid DCs (pDC) via the TLR9/MyD88-dependent viral recognition, thus leading to the activation of interferon regulatory factor 7 and the promotion of the IFN-alpha/IFN-gamma-dependent effector pathway, which resulted in vivo in protection against primary murine cytomegalovirus infection; (c) induced indoleamine 2,3-dioxygenase activity in DCs, thus affecting tolerization toward self as well as microbial non-self-antigens, and

this resulted in vivo in transplantation tolerance and protection from inflammatory allergy. Talpha1 is produced in vivo by cleavage of prothymosin alpha in diverse mammalian tissues. Our data qualify Talpha1 as an endogenous regulator of immune homeostasis and suggest that instructive immunotherapy with Talpha1, via DCs and tryptophan catabolism, could be at work to control inflammation, immunity, and tolerance in a variety of clinical settings.

Full Text Not Available

Panatto D, et al. **Utility of thymosin alpha-1 (Zadaxin) as a co-adjuvant in influenza vaccines: a review.** J Prev Med Hyg. 2011;52(3):111-5.

LEVEL 8

Abstract: Influenza constitutes a serious problem for healthcare and social services worldwide, owing to its pattern and the severity of its complications in some categories of subjects at risk, such as the elderly and immunocompromised individuals. The only really effective means of combating influenza is vaccination. The elderly and immunocompromised subjects are refractory or low responders to vaccination. The need for ever more immunogenic and efficacious influenza vaccines, especially for subjects at risk, has prompted the development of adjuvated vaccines. With a view to enhancing the immune response in the elderly and in subjects at risk, the possibility of co-administering immunostimulants as Thymosin alpha-1 (Talpha1) with influenza vaccines has been investigated. Talpha1 is a biologically active peptide made up of 28 amino acids that can enhance T-cells, dendritic cell and antibody responses, modulate cytokines and chemokines production. Several studies were conducted and showed that Talpha1 ameliorate the performanc of influenza vaccination in elderly and subjects at risk. Although further studies on co-adjuvants are necessary, the future prospects of producing ever more efficacious influenza vaccines appear very promising.

No Full Text Available

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