



Review

Thymic Peptides and Preparations: an Update

OSCAR J. CORDERO, ALICIA PIÑEIRO and MONTSERRAT NOGUEIRA

Department of Biochemistry and Molecular Biology, University of Santiago de Compostela, 15706 Santiago de Compostela, Spain

Abstract. The possibilities of thymic peptides in human therapy are still being described. Here, we focus on their general characteristics and on recent advances in this area.

Key words: thymus; thymic peptides; preclinical investigation; therapeutic use; clinical trials.

Thymic peptides, as well as a variety of other modulators (IL-1, IL-3, IL-6, GM-CSF) and cell-cell interactions, regulate the process known as thymic selection by which pro-thymocytes become mature and functional T cells.

Several polypeptides have been extracted, mainly from young calves, and some of them have been successfully isolated and prepared synthetically (Fig. 1). The precise role of much of these factors purported to have intrathymic effects is still unknown, although many of these compounds exhibit immunobiological activity. On the basis of this fact, several clinical applications of thymic peptides have been studied recently, revealing a promising new field in the development of therapeutic drugs, as positive results have been obtained, i. e., on cancer and some immunodeficiencies.

Thymulin

Thymulin (TH) is a nonapeptide that is biologically active only when it is coupled with zinc. Initially, it was

purified from porcine and human serum and from calf thymus, and named “facteur thymique serique”¹¹.

According to the classical criteria, TH is the unique peptide that can be recognized as a hormone. Its secretion by a subpopulation of thymic epithelial cells (TEC) is controlled by a pleiotropic mechanism involving its own levels and those of prolactine (PRL), growth hormone (GH) through insulin growth factor 1 (IGF-1) secretion, adrenocorticotropin (ACTH), thyroxin (T₄), β -endorphin and β -leukencephalin and IL-1 α and β ⁸.

Furthermore, reciprocal regulatory actions on the hypothalamus-pituitary axis have been proposed, based on results suggesting that TH might modulate the secretion of ACTH, luteinising hormone (LH) and PRL^{19, 21}. In addition to this function as transmitter between the neuroendocrine and the immune system, TH exerts many other functions ranging from differentiation of immature thymocytes to immune modulation. This is reflected by the fact that Crohn’s disease or acute lymphoblastic leukemia patients share Zn⁺² and TH activity deficits. Likewise, people suffering myasthenia gravis show an impairment in both Zn⁺² and TH,

Abbreviation used: IL – interleukin, GM-CSF – granulocyte/macrophage-colony stimulatory factor, TEC – thymic epithelial cells, GH – growth hormone, IGF-1 – insulin growth factor-1, ACTH – adrenocorticotropin, T₄ – tiroxin, LH – luteinising hormone, PRL – prolactine, TNF – tumor necrosis factor, PBMC – peripheral blood mononuclear cells, HIV – human immunodeficiency virus, IFN – interferon, NK – natural killer, HBV – hepatitis B virus, HBeAg – hepatitis Be antigen, AZT – azidodeoxithimidine/zidovudine, PHA – phytohemagglutinin.

but in this case an age-dependent mechanism also seems to be involved²⁴.

Recent data indicate that TH can be therapeutically effective in preventing the development of rheumatoid arthritis². Likewise, its role in hyperalgesia is being investigated at the moment^{32, 33}.

In rats immune to viral oncogene products, TH augments suppressive effects on tumor development²⁸. In the same way, the animal models of acute graft-versus-host disease studied have shown that TH has a protective effect in mice's enteropathy; so, it has been recently proposed as a possible therapeutic agent in acute graft-versus-host disease after blood transfusion or bone marrow transplantation in humans²³.

Thymic Humoral Factor

This crude extract was obtained from calf thymus, after which the octapeptide thymic humoral factor (THF)- $\gamma 2$ was isolated from it using chromatography. Both share the same properties, namely, to have stimulatory effects on myeloid and erythroid hematopoietic progenitor cells and to enhance lymphocyte proliferation and IL-2 production by spleen cells from neonatally thymectomized mice or from immunocompromised patients' lymphocytes⁹.

An antiviral effect can be proposed for THF- $\gamma 2$ *in vivo*, if we consider both that it diminishes murine cytomegalovirus infection and also that it increases production of IL-2 and TNF- α in PBMC obtained from patients with chronic hepatitis B.

A. Thymulin (FTS)
QAKSQGGSN

B. Thymic humoral factor (THF) – it is an extract
B. 1. THF- $\gamma 2$
LEDGPKFL

C. Thymopoietin (TP)
GLPKEVPAVL TKQKLKSELV ANGVTLPAGE
MRKDVYVELY LQHLTALH
C.1. TP-5
RKDVY

D. Thymosins (T)
D.1. ProT α
SDAAVDTSSSE ITTKDLKEKK EVVEEAENGR
DAPANGNANE ENGEQEADNE VDEEEEEEGGE
EEEEEEEGDG EEEDGDEDEE AESATGKRAA
EDDEDDVDVT KKQKTDEDD
D.2. T α_1
SDAAVDTSSSE ITTKDLKEKK EVVEEAEN

Fig. 1. The amino acid sequences of the thymic peptides

In addition to this possible function, THF- $\gamma 2$ restores immunocompetence and reduces metastasis in tumor-bearing mice receiving anticancer immunotherapy¹⁰.

Recently, a clinical trial has been developed which concludes that THF- $\gamma 2$ administered with zidovudine reduces the number of opportunistic infections in HIV patients naive for antiretroviral therapy and it increases their survival time²⁵.

Thymopoietin

Thymopoietin (TP) was isolated from calf thymus for its neuromuscular effects, but nowadays its immunomodulatory function is recognized too.

In spite of its abundant presence on thymocytes, TP appears in TEC, primary and secondary lymphatic tissues and in non lymphatic tissues (striated muscle, heart, small intestine and cerebellum). A role in the regulation of thymocyte differentiation and T lymphocyte proliferation has been described; in the same way it has been recently described as an inducer of human TEC proliferation²⁰.

Many evidences – including its interaction with lamina B₁³⁸ – suggest that it plays a nuclear role, probably in proliferation and cell cycle control⁹.

Thymopoietin has 49 amino acids and its biological activity is comprised in the pentapeptide composed of residues 32 to 36, named Thymopentin (TP-5). Interestingly, there is a thymopentin-like motif which seems to account for the immunomodulatory activity of G-actin³⁶.

TP-5 is the only thymic peptide approved as a single drug, and it is applied in the therapy of primary immunodeficiencies.

Recently, a phase III trial showed that dose-intensified chemotherapy can be used safely and effectively on pre-treated patients of breast, gastric and small cell lung cancer, if TP-5 and G-CSF are used as support³¹.

In spite of its good immunostimulatory results, TP-5 has as disadvantage its limited half-life in plasma. Attempts to resolve this have taken different approaches. Stabilized analogues of TP-5 via insertion of ketomethylene have been tested *in vivo* showing immunopotentiating properties (induction of Thy-1.2 expression and stimulation of T cell proliferation) as well as they exhibited disease remitting properties in two animal models of arthritis^{12, 13, 37}. Good results of prevalence were also obtained by preparing liposomes³⁰ or embedding the drug in polymeric matrix microspheres⁷.

In atopic eczema, TP-5 has also shown convincing results in many different trials, being safe and effective

in the improvement of clinical symptoms. Nevertheless, therapeutic benefits of TP-5 in this affection have not taken to general acceptance, a surprising fact if we consider that classical treatments have shown high adverse side effects^{6, 26}.

Thymosins

Thymosins were originally isolated from a partially purified bovine thymic extract, "named" thymosin fraction V (TF-V). TF-V showed immunostimulatory activity, restoring abnormalities in thymic weight and in diseases as Di George syndrome. At least 30 peptides belonging to the α or β thymosins family can be identified by isoelectric focusing of TF-V; from them, thymosin α_1 ($T\alpha_1$) and thymosin β_4 ($T\beta_4$) retain the major activity of the original fraction³.

$T\alpha_1$ is a highly conserved 28 amino acid peptide which contains most of the activity of TF-V; it is a potent immunostimulator with a very important advantage, its low toxicity compared to other response modifiers as ILs or IFN- γ . In lymphocytes, it induces differentiation (as seen from Thy1/Lyt1 and Lyt2,3 expression) increases responses to mitogens and enhances production of antibodies and many cytokines (IFN- α , IFN- γ , IL-2, IL-3, IL-4). It also augments expression of cytokine receptors and NK cell activity.

Preclinical investigation reports many possible applications of $T\alpha_1$. In addition to the classical descriptions of protection from *C. albicans* infection, it also enhances resistance to other infections such as *H. simplex*, *L. monocytogenes* and *P. aeruginosa* in immunosuppressed animals. Another promising results are those taken out from pilot studies with autoimmune disease patients in which $T\alpha_1$ was given as an adjuvant in influenza vaccination, obtaining good protection in elderly people¹⁸. These studies had their precursors in other where, when applied as pretreatment on aged mice, high protection was obtained¹⁶.

On non-small cell lung cancer cell-lines, $T\alpha_1$ showed an inhibitory effect on cell growth as its analogue $T\alpha_1$ -amida did, both *in vitro* and *in vivo*²⁹.

One of the most promising therapeutical applications of $T\alpha_1$ are the ongoing trials on the treatment of hepatitis B, C and D. Encouraging results are being obtained around the world both with $T\alpha_1$ alone and with $T\alpha_1$ combined therapies.

As a single drug in hepatitis B therapy, $T\alpha_1$ has rendered 25% loss of serum HBV DNA while placebo only 13%. In this phase III multicenter trial, patients received $T\alpha_1$ biweekly for 6 months and were followed monthly for a one-year period¹⁸.

Similar trials are being performed in Singapore, Taiwan and Japan²², due to the great sanitary problem that HBV represents in Asian countries. In Taiwan, 33.3% of patients lost DNA and seroconverted for HBeAg in a 6-month treatment and 38.5% in a 12 month one, whereas the control group only did it in 8.3%.

Phase III trials being undertaken at Singapore and Japan are refining the use of this drug, as far as the dose-ranging efficacy and effectiveness in a broader group of patients.

The Italian National Research Council²² has also sponsored a pilot trial of combination therapy with $T\alpha_1$ and IFN- α , being given to chronic hepatitis B patients. The data indicate a conversion rate to negative status in 40% subjects.

Even more, in a US multicenter trial beneficial results on IFN- α / $T\alpha_1$ combination therapy for the treatment of hepatitis C infection were reported. This approach revealed higher efficacy than with the use of IFN- α_{2b} or placebo alone in terms of biochemical, histological and virological end-treatment responses³⁵. In a previous pilot trial, $T\alpha_1$ alone did not show any remarkable effect, suggesting a synergism between $T\alpha_1$ and IFN- α_{2b} ¹.

In HIV infection, the immune response has to be restored, so it seems reasonable to take on an approach of using immunorestorative drugs as therapy. A phase III trial has been concluded in Italy on HIV positive patients; the subjects were treated with different combinations of AZT, IFN and $T\alpha_1$ and a significant increase in CD4 count was obtained when the 3 drugs were used as a whole¹⁷.

There have been other successful approaches to the clinical applications of $T\alpha_1$ as combined therapy for non-small cell lung cancer and melanoma in phase II trials, and their corresponding phase III studies are still going on¹⁸.

Prothymosin α

Prothymosin α (Pro $T\alpha$) was first isolated as the putative precursor of $T\alpha_1$ and its family of related peptides. Later, all the α thymosins were proposed as degradative fragments of Pro $T\alpha$ and a hot spot was established that today remains unfinished. This highly acidic polypeptide of 109 amino acids (bovine or human origin) contains $T\alpha_1$ at its N-terminal region, and is detected in a large variety of cell types and tissues and widely distributed among vertebrates. Pro $T\alpha$ appears at great concentrations in the thymus cortex and it is detected in human serum, too. Although this might indicate its secretion, the existence of a putative

nuclear targeting sequence and observations on its mRNA according to the cell cycle might suggest a nuclear role, as well. Both evidences on nuclear and cytoplasmic locations have been found^{9, 10}. ProT α protects against *C. albicans* as T α_1 does, but in a very much lower dose (this could be another probe pointing at T α_1 as a decay product). Many *in vitro* effects of ProT α have been described including: NK enhanced activity, antitumoral increased activity of melanoma patients' monocytes, enhanced secretion of IL-2 and proliferation of PHA stimulated PBMC, enhanced response of T cell proliferative to soluble antigens and enhanced expression of HLA-DR antigen in monocytic cell lines and in cultivated monocytes. All of these constitute a great evidence for the potential immunopharmacological properties of ProT α in cancer or autoimmune disease therapies, which can be confirmed by *in vivo* ProT α 's effects. It exerts a great immunostimulatory activity both in aged and young rats, increases the *in vivo* production and release of migratory inhibitory factor (MIF), enhances the proliferative responses in autoimmune diseases patients and shows antitumoral activity in mice injected with leukemic cells³⁹. The most recent *in vitro* studies on ProT α are those made on peripheral blood lymphocytes from colorectal tumor patients where, in combination with IL-2, lymphocyte deficiencies can be at least partially restored¹⁵. This kind of works suppose the first step to therapeutical applications of this thymic peptide. We can conclude that, in spite of being one of the newest thymic peptides, ProT α has given promising results, so further investigation is required including reliable clinical trials.

Thymic Preparations

As happens with other biological response modifiers, thymic peptides have rendered very good results when used in synergistic combinations. In this sense, some mixtures have been obtained with a relatively successful application. One of them is thymostimulin (TP-1) which has been applied in atopic eczema as TP-5 with similar results²⁶. In addition, clinical trials have been developed in immunostimulatory activity of TP-1 before chemotherapy on head and neck carcinoma patients¹⁴ and on chronic obstructive pulmonary preventing exacerbation of this disease⁵. More on, *in vitro* experiments demonstrate that it increases natural cytotoxic activity in breast cancer patients who have been subjected to chemotherapy²⁷. Finally, in a small pilot study, it was shown that TP-1 alone induced tumor regression in one half of the hepatocellular cancer pa-

tients treated and an *in vitro* study has established that it occurs through activation of Kupffer cells and concomitant release of TNF- α ; this was the basis for a phase I trial in current development⁴.

Another thymus extract, TFX-thymomodulin, has improved bactericidal capacity of polymorphonuclear neutrophils in malnourished infants, being a possible insight to clinically restore their impaired immune response⁴⁰. Separately, TFX and Thymex-L (a thymorgan GmbH commercial thymic preparation) alone or in combination were given in addition to standard therapy to patients with severe burns in a controlled clinical trial. The best results were obtained when both were used at a time, increasing the survival rate and shortening the period of healing surface and deep burns³⁴. Once more, the immunostimulatory and restorative properties of thymic preparations are stood out, as well as others like regenerating effects on cells, organs and vascular tissues.

In conclusion, all the clinical and preclinical evidences point toward an important role for thymic peptides for future therapeutic treatments. The most outstanding results are those obtained of combined therapies, perhaps due to the complexity of these illnesses and their disturbed biological equilibrium indicating a need to take on a multistep outlook in order to obtain positive results. Therefore, we can conclude that when designing future strategies to treat the diseases of our times, thymic peptides should, without a doubt, be included.

References

1. ANDREONE P., CURSARO C., GRAMENZI A., BUZZI A., COVARELLI M. G., DI GIAMMARINO L., MINIERO R., ARIENTI V., BERNARDI M. and GASBARRINI G. (1996): A double-blind placebo-controlled, pilot trial of thymosin alpha 1 for the treatment of chronic hepatitis C. *Liver*, **16**, 207–210.
2. AONO H., MORISHITA M., SASANO M., OKAMOTO M., OKAHARA A., NAKATA K. and MITA S. (1997): Amelioration of type II collagen induced arthritis in rats by treatments with thymulin. *J. Rheumatol.*, **24** (8), 1564–1569.
3. BACH J. F. (1986): The role of thymic hormones in T cell differentiation: an overview. In GOLDSTEIN G., BACH J. F. and WIGZELL H.: *Immune regulation by characterized polypeptides*. Alan R. Liss, New York, 245–258.
4. BALCH G., IZZO F., CHIAO P., KLOSTERGAARD J. and CURLEY S. A. (1997): Activation of human Kupffer cells by thymostimulin (TP-1) to produce cytotoxicity against human hepatocellular cancer. *Ann. Sur. Oncol.*, **4** (2), 149–155.
5. BANOS V., GÓMEZ J., GARCÍA A., RUIZ J., ALVAREZ R., LORENZO M., CANTERAS M. and VALDES M. (1997): Effectiveness of immunomodulating treatment (thymostimulin) in chronic obstructive pulmonary disease. *Respiration*, **64** (3), 220–223.

6. BREHLER R., HILDEBRAND A. and LUGER T. A. (1997): Recent developments in the treatment of atopic eczema. *J. Am. Acad. Dermatol.*, **36** (6 Pt 1), 983–994.
7. CONTI B., PANICO M., VENTURA C. A., GIUNCHEDI P. and PUGLISI G. (1997): Thymopentin loaded by w/o/w emulsion technique: *in vitro/ex vivo* evaluation. *J. Microencapsul.*, **14** (3), 303–310.
8. CORDERO O. J., MAURER H. R. and NOGUEIRA M. (1997): Novel approaches to immunotherapy using thymic peptides. *Immunol. Today*, **18**, 10–13.
9. CORDERO O. J. and NOGUEIRA M. (1998): Thymic hormones and peptides. In DELVES P. J. and ROITT I. M.: *Encyclopedia of immunology*. 2nd ed. Academic Press, London, 2300–2304.
10. CORDERO O. J. and NOGUEIRA M. (1999): Thymic peptides. In McGraw-Hill 1999 yearbook of science and technology. McGraw-Hill, New York, 171–172.
11. DARDENNE M. and BACH J. F. (1988): Functional biology of thymic hormones. In KENDALL M. D. and RITTER M. A.: *Thymus update 1. The microenvironment of the human thymus*. Harwood Academic Publications, London, 101–116.
12. DE GRAW J. I., ALMQUIST R. G., HIEBERT C. K., COLWELL W. T., CRASE J., HAYANO T., JUDD A. K., DOUSMAN L., SMITH R. L., WAUD W. R. and UCHIDA I. (1997): Stabilized analogues of thymopentin. 1. 4,5-ketomethylene pseudopeptides. *J. Med. Chem.*, **40** (15), 2386–2397.
13. DE GRAW J. I., ALMQUIST R. G., HIEBERT C. K., JUDD A. K., DOUSMAN L., SMITH R. L., WAUD W. R. and UCHIDA I. (1997): Stabilized analogues of thymopentin. 2. 1,2-ketomethylene and 3,4-ketomethylene pseudopeptides. *J. Med. Chem.*, **40** (15), 2398–2406.
14. DE-SERDIO J. L., VILLAR A., ALVAREZ I. E., GIL-CUBELO J. A., SNER M., HERNÁNDEZ R. and LÓPEZ-AGUADO D. (1997): The effects of thymostimulin in a protocol of concurrent hyperfractionated carboplatin and irradiation. *Acta Otorrinolaringol. Esp.*, **48** (6), 487–492.
15. ECKERT K., GRUNBERG E., IMMENSCHUH P., GARBIN F., KREUSER E. D. and MAURER H. R. (1997): Interleukin-2-activated killer cell activity in colorectal tumor patients: evaluation of *in vitro* effects by prothymosin α_1 . *J. Cancer Res. Clin. Oncol.*, **123** (8), 420–428.
16. EFFEROS R. (1988): The effect of thymosin α_1 on immunity to influenza in aged mice. *Aging*, **1**, 31–40.
17. GARACI E., ROCCHI G., PERRONI L., D'AGOSTINI C., SOSCIA F., GRELLI S., MASTINO A. and FAVALLI C. (1994): Combination treatment with zidovudine, thymosin α_1 and interferon- α in human immunodeficiency virus infection. *Int. J. Clin. Lab. Res.*, **24**, 23–28.
18. GOLDSTEIN A. L., BADAMCHIAN M., PAINO J., BAUMANN C. A., MORA C. and HORWITZ D. (1997): Thymosin α_1 . Current status of human trials and potencial applications in clinical therapy. In MAURER H. R., GOLDSTEIN A. L. and HAGER E. D.: *Thymic peptides in preclinical and clinical medicine. An update*. W. Zuchschwerdt Verlag, München, 131–154.
19. GOYA R. G., SOSA Y. E., BROWN O. A. and DARDENNE M. (1994): *In vitro* studies on the thymus-pituitary axis in young and old rats. *Ann. NY Acad. Sci.*, **741**, 108–114.
20. GUERIN S., MARI B., FERNÁNDEZ E., BELHACENE N., TORIBIO M. L. and AUBERGER P. (1997): CD10 is expressed on human epithelial cell lines and modulates thymopentin-induced cell proliferation. *FASEB J.*, **11** (12), 1003–1011.
21. HADLEY A. J., RANTLE C. M. and BUCKINGHAM J. C. (1997): Thymulin stimulates corticotrophin release and cyclic nucleotide formation in the rat anterior pituitary gland. *Neuroimmunomodulation*, **4** (2), 62–69.
22. HORWITZ D. L. (1997): Results of clinical trials of thymosin α_1 in chronic hepatitis B conducted in Taiwan, Singapore, Japan and Italy. In MAURER H. R., GOLDSTEIN A. L. and HAGER E. D.: *Thymic peptides in preclinical and clinical medicine. An update*. W. Zuchschwerdt Verlag, München, 162–167.
23. INAGAKI-OHARA K., SAKAI T., KOYA G., AWAYA A. and YOSHIKAI Y. (1997): A thymic hormone protects mice from enteropathy during acute graft-versus-host disease. *Microbiol. Immunol.*, **41** (11), 883–889.
24. LICASTRO F., MOCCHIGIANI E., FABRIS N., RINALDI R., BONTEMPO G., TONON C., SCHIAVINA M., COSTA A. N. and D'ALESSANDRO R. (1997): Altered thymic endocrine activity along with impairments of peripheral zinc metabolism and T-lymphocyte populations are associated with myasthenia gravis: a follow up study. *J. Neuroimmunol.*, **77** (2), 153–160.
25. MAGGIOLO F., TARAS A., PRAVETTONNI M. G., LEONE M., INGROSSO A. and SUTER F. (1997): Zidovudine and thymus humoral factor gamma-2 in the treatment of HIV infection: preliminary clinical experience. *Infection*, **25** (1), 35–38.
26. MAURER H. R. (1997): Thymic peptides for therapy of atopic dermatitis (neurodermitis). A review. In MAURER H. R., GOLDSTEIN A. L. and HAGER E. D.: *Thymic peptides in preclinical and clinical medicine. An update*. W. Zuchschwerdt Verlag, München, 114–121.
27. MENESES G., DELGADO M. A., PÉREZ-MACHADO M. A., PRIETO A., ALONSO R., CARRION F., LANZOS E. and ALVAREZ-MON M. (1997): Thymostimulin increases natural cytotoxin activity in patients with breast cancer. *Int. J. Immunopharmacol.*, **19** (4), 187–193.
28. MIYAUCHI M., KOSHIKAWA N., KOWAMURA K., FUKUSHIMA T., MOCHIZUKI S., AWAKA A. and MARUYAMA K. (1997): Augmentation with serum thymic factor of suppressive effects on retroviral tumor development in hosts immune to v-onc product. *Leukemia*, **11** (suppl. 3), 213–215.
29. MOODY T. W., FAGARASAN M. and GOZES Y. (1997): Inhibition of non-small cell lung cancer growth by thymosin α_1 analogues. In MAURER H. R., GOLDSTEIN A. L. and HAGER E. D.: *Thymic peptides in preclinical and clinical medicine. An update*. W. Zuchschwerdt Verlag, München, 77–88.
30. PANICO A., PIGNATELLO R., CARDILE V. and PUGLISI G. (1997): Preparation of liposome formulations containing immunomodulatory peptides. *Pharm. Acta Helv.*, **72** (1), 1–10.
31. RECCHIA F., DE FILIPPIS S., GINALDI L., QUAGLINO D., GULINO A., FRATI L. and REA S. (1997): Phase I–II study of dose intensified chemotherapy with filgrastim and thymopentin in patients with advanced cancer. *Clin. Ther.*, **148** (5–6), 201–207.
32. SAFIEH GARABEDIAN B., KANAAN S. A., JALAKHIAN R. H., JABBUR S. J. and SADE N. E. (1997): Involvement of interleukin-1 beta, nerve growth factor and prostaglandin-E₂ in the hyperalgesia induced by intraplantar injections of low doses of thymulin. *Brain Behav. Immunol.*, **11** (3), 185–200.
33. SAFIEH GARABEDIAN B., KANAAN S. A., JALAKHIAN R. H., POOLE S., JABBUR S. J. and SADE N. E. (1997): Hyperalgesia induced by low doses of thymulin injection: possible involvement of prostaglandin-E₂. *J. Neuroimmunol.*, **73** (1–2), 162–168.
34. SAKIEL S., CZAPLICKI J., BLONSKA B., UCHMAN M., CZARNECKI J. and PESIC M. C. (1996): Thymic preparations. A promising

- addition to treatment of patients with severe burns. *Int. J. Thymol.*, **4** (suppl. 1), 6–17.
35. SHERMAN K. E. (1997): A phase III trial of interferon α /thymosin α_1 combination therapy for hepatitis C in the United States. Interim results. In MAURER H. R., GOLDSTEIN A. L. and HAGER E. D.: *Thymic peptides in preclinical and clinical medicine. An update.* W. Zuchschwerdt Verlag, München, 154–161.
36. SIEMION I. Z., STRUG I., WYSŁOUCH-CIESZYŃSKA A., NOWAK E. and WIECZOREK Z. (1997): Immunomodulatory activity of G-actin fragments containing a thymopentin-like sequence. *Arch. Immunol. Ther. Exp.*, **45** (5–6), 419–425.
37. SMITH R. L., DOUSMAN L., WAUD W. R. and DE GRAW J. I. (1997): Stabilized analogues of thymopentin. 3. Evaluation of ketomethylene pseudopeptides for antiarthritic properties. *J. Med. Chem.*, **40** (15), 2407–2411.
38. THEODOR L., SHOHAM J., BERGER R., GOKKEL E., TRACHTENBROT L., SIMON A. J., BROK-SIMON F., NIR U., ILAN E., ZEVIN-SONKIN D., FRIEDMAN E. and RECHARI G. (1997): Ubiquitous expression of a cloned murine thymopoietin cDNA. *Acta Haematol.*, **97** (3), 153–163.
39. VUCOVIC-DEKIC L. and STAJNOJEVIC-BAKIC N. (1997): Prothymosin alpha-1 as a biological response modifier. *Int. J. Thymol.*, **5** (8–9), 399–408.
40. WYSOCKI J. (1995): The influence of thymus extract on the phagocytosis and the bactericidal capacity of polymorphonuclear neutrophils from malnourished infants. *Int. J. Thymol.*, **3** (6), 304–307.

Received in August 1998

Accepted in October 1998