

Sixth International Symposium on Thymosins in Health and Disease

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Abstract: “Thymosins in Health and Disease” are periodic symposia whose aim is to bring together many of the leading researchers from the United States, Europe, and Asia to report on the advances being made in the chemistry, biology, and clinical applications of thymosins. The first edition took place in Washington in 2007. The article describes the latest sixth edition this international symposium.

Keywords: symposium, thymosins, thymosin $\alpha 1$, thymosin $\beta 4$, TFX®, immunology, oncology, clinical trials

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This year’s meeting took place in Rome, Italy from 20th to 22nd of October 2022. Main topics of plenary sessions and poster session covered mostly mechanisms of actions, preclinical and clinical use of thymosin $\alpha 1$ and thymosin $\beta 4$ as well as other immune-related topics.

Introductory remarks were given on 20th October by professors Allan L. Goldstein from The George Washington University, Washington D.C., and Enrico Garaci from University of Rome San Raffaele, Rome. Prof. Garaci was happy to organize the conference despite COVID-19 related difficulties. He saw hope in the increasing number of clinical trials of thymosin-related treatments. Prof. Goldstein welcomed all both on place and attending via the Internet - scientists from 12 countries who shared their research.

The first keynote speech was given by dr. Anna Teresa Palamara who was honored with Abraham White’s Public

Service Award for her pioneering studies and scientific contributions in the fields of immunology and virology, and her leadership in improving the public health system in Italy to curb the COVID-19 epidemic. Her work was dedicated to establishing a genomic laboratory network in Italy and creating a surveillance network to build an early COVID-19 alert system. During her talk she discussed the beginning and development of pandemy in Italy, pathogenicity of SARS-CoV-2 - how different variants operate in different ways resulting in different severity illness as well as treatment using thymosin $\alpha 1$, especially before effective drugs and vaccines were available.

The second keynote speech was given by dr. Ildiko Bock-Marquette who was honored with Abraham White’s Scientific Award for her pioneering studies and scientific contributions which have significantly advanced our understanding of the role of thymosin $\beta 4$ in both embryonic

development and during aging process. Her speech was centered around the heart. In mice embryos studies, both in vitro and in vivo, T β 4 promotes myocardial cell migration and survival in embryonic tissue. In adults after coronary artery ligation the peptide enhanced myocyte survival and improved cardiac function and reactivated embryonic program resulting in thickening of epicardial monolayer in damaged and healthy areas. Conclusion was T β 4 is crucial during early development but also postnatal administration might reverse aging processes.

The first plenary session was on 21st October and presented research focused on T α 1 application. L. Liu showed how overall survival in patients with non-small lung cancer might be improved with administration of thymus peptide if cancer was resected. Another result was confirmation of improving patients' immunity and contributing to the anti-cancer effects with current therapeutic regimens. In another presentation, E. Nizri from Tel-Aviv University showed how heated intraperitoneal chemotherapy, which is currently implied in the treatment of peritoneal metastases from colorectal carcinoma origin can be enhanced with T α 1. An increase in the number of T helper cells caused by thymosin strengthens anti-tumor immune response.

The second plenary session was centered around thymosin beta 4. H. Kleinman from National Institutes of Health Bethesda, MD overviewed the role of T β 4 in preventing fibrosis or scarring in various organs such as heart, liver, skin, kidney and lung. The mechanism of action appears related, to a reduction in the inflammatory response, including a reduction in macrophage infiltration, decreased levels of TGF β and IL-10 and reduced CTGF activation, resulting in both prevention of fibroblast conversion to myofibroblasts and production of normally aligned collagen fibers. During the same session P. Bako from University of Pecs, Hungary discussed the role of thymosin β 4 in healing middle ear lesions in mammals. His team discovered that peptide affects the behavior of epidermal and epithelial cells of the tympanic membrane in vitro. Moreover, it is not the differentiated, but most likely the local epidermal progenitor cells which are the primary targets of the molecule.

The next plenary session was almost dominated with research on T α 1 treatment in patients with COVID-19. Although each researcher focused on different aspects, the conclusion was similar: thymosin is useful in COVID-19 as it reduces pro-inflammation cytokines and prevents severe course of disease. H. A. Drexhage from Erasmus University Medical Center Rotterdam, Netherlands, presented ongoing study of using thymosin- α 1 treatment to correct the reduced numbers of naive cd4+ t cells and the low-grade inflammation in patients with major depression. The main study endpoint will be an increase in the relative number/percentage of (naive) CD4+ T cells (and as a consequence a restoration of the decreased (naive)

CD4+/CD8+ T cell ratio). Secondary outcomes include changes in depression, anxiety, fatigue and quality of life scores, as well as changes in levels of markers of inflammation, such as the hCRP and IL-6 serum levels and the monocyte inflammatory gene expression.

During the poster session mostly research of young academics was presented. Among these presentations was a memorial for dr. Luc Montagnier by Adan Rios from UT McGovern Medical School at Houston, Texas. Montagnier's work has expanded from the discovery of HIV to an influence in the understanding of the immune system, including the popularization of immunological methodologies.

In the evening an award banquet was held and in addition to the previously mentioned awardees, also James E. Talmadge and archbishop Vincenzo Paglia were given awards. Talmadge was granted a science award for his lifetime of scientific discoveries in fields of immunology and cancer research. Among them were demonstration that spontaneous metastasis originates from clonal subpopulation of cells within primary tumor and discovery and development of a number of novel cytokine, hematopoietic and anti-inflammatory drugs that have benefited millions of children and adults worldwide. He also gave a speech about highlights into historical and current immune interventions for cancer that evening. Second awardee, in the humanitarian field, was archbishop Paglia for his long and distinguished humanitarian service on behalf of peace, dialogue, bioethics, and the promotion of human dignity. His latest achievement was, as president of the Pontifical Academy for Life, to issue a joint paper with Vatican COVID-19 Commission confirming the moral responsibility that individuals have to take COVID vaccines and outlining the responsibilities of nations to make vaccines available to all.

The first session on Saturday included two especially interesting speeches. First of them, by dr. Joanna I. Lachowicz from the Department of Medical Sciences and Public Health, University of Cagliari, Italy, explored metal-driven biochemistry of thymosin β 4. Presented data supported the hypothesis that the essential metal ions coordination is a driving force in T β 4 ferroptosis switching and cellular translocation, with further influences on tissue development and regeneration, tumor metastasis, and neurodegeneration. Another one was by prof. Aleksander B. Skotnicki from Department of Hematology Jagiellonian University, Kraków, Poland, who gave an overview on immunological activity of calf thymus extract TFX[®] and its therapeutic benefits. He pointed out that TFX[®] is a safe, non-toxic preparation of thymic hormones from juvenile calves' thymic glands, capable of restoring immune system functions in immunocompromised animals and patients by acting not only on immature T cells but also indirectly on maturation and function of other cell types. TFX[®] is a mixture of naturally occurring thymus peptides with a

molecular weight of less than 10 kDa and contains, among others, thymosin beta 4 and thymosin alpha 1, so it shows all the activities of these peptides, as well as the additional benefits of a complex drug composition. Professor Skotnicki explained that the use of multicomponent preparations is more beneficial due to the differentiation of the biological effects of their individual components, which translates into a better immunocorrective or reconstructive effect. In addition, thymus peptides of natural origin contain complex substances that, when applied, cause a tissue-specific trophic effect on the thymus, restore T cells function, and host immunity. All these features mean that TFX® can exhibit bidirectional immunomodulatory activity on the biological response, because on the one hand, it increases the activity of cytotoxic CD8+ lymphocytes, and on the other - by affecting the functions of regulatory T cells - it controls and inhibits excessive auto- and alloreactivity. Thymotherapy is physiological and responds to the systemic homeostatic "demand" by regulating existing disorders.

During the last plenary session Nicola Smart from Department of Physiology, Anatomy & Genetics, Univer-

sity of Oxford, United Kingdom, showed how thymosin β 4 preserves vascular smooth muscle cell phenotype in atherosclerosis via regulation of low density lipoprotein receptor related protein. Besides presenting a poster earlier, Adan Rios also gave a speech on secondary hemophagocytic lymphohistiocytosis. Secondary HLH has pleiotropic manifestations and is part of a spectrum of hyperactivation syndromes of the immune system which includes MAS (macrophage activation syndrome), graft vs host disease (GVH), and checkpoint immune inhibitors toxicities among others. Often a central feature of its presentation is in the form of a cytokine storm. Recent investigations have shown the potential for Thymosin α 1 in controlling the immune response and cytokine storm.

In the end professors Garaci and Goldstein gave closing remarks expressing great joy of success which was Sixth International Symposium on Thymosins in Health and Disease and hoped for hosting the next symposium with an even greater number of participants and even more advanced research breakthroughs.

Table 1. Lectures presented at the Sixth International Symposium on Thymosins in Health and Disease. Selected speeches are discussed in more detail in the text.

October 20, 2022	
KEYNOTE SESSION	
Anna Teresa Palamara	SARS-CoV-2: Lessons from a pandemic virus
Ildiko Bock-Marquette	Thymosin β 4 denotes new directions towards developing prosperous anti-aging regenerative therapies
October 21, 2022	
PLENARY SESSION I: Thymosin α1 – preclinical & clinical applications: immune modulation, infectious diseases, septic shock, cystic fibrosis, and cancer	
Li Mao	Thymosin α 1 – reimagine its broader applications in the immunoncology era
Lu Ke	Immune enhancement in patients with predicted severe acute necrotizing pancreatitis
Lunxu Liu et al.	Impact of thymosin α 1 as an immunomodulatory therapy on long-term survival of NSCLC following R0 resection: A propensity score-matched
Jianfeng Wu, Fei Pei, & Xiangdong Guan	The efficacy and safety of thymosin α 1 for sepsis (TESTS): A randomized, double-blind and placebo-controlled clinical trial
Eran Nizri et al.	Thymosin α 1 as an adjuvant to hyperthermic intraperitoneal chemotherapy in an experimental model of peritoneal metastases from colonic carcinoma
Giorgia Renga et al.	Thymosin α 1 protects from CTLA-4 intestinal immunopathology
Claudio Constantini, Giovanna Pisi, et al.	A phase II trial to assess the activity and tolerability of thymosin α 1 in cystic fibrosis patients

PLENARY SESSION II: Thymosin β4 – clinical applications in inflammatory and infectious diseases, fibrosis, sepsis, Alzheimer’s disease, wound healing, and dry eye	
Peter Bako et al.	The role of thymosin β 4 in healing middle ear lesions in mammals
Youngmi Jung & Jieun Kim	Thymosin β 4 influences liver fibrosis by regulating activation of hepatic stellate cells in mice with liver injury
Elizabeth Berger et al.	Adjunctive thymosin β 4 treatment influences innate immune effector cell function during <i>Pseudomonas aeruginosa</i> -induced corneal infection
Gabriel Sosne et al.	Thymosin β 4: A novel adjunct treatment for bacterial keratitis
Hynda K. Kleinman, Veronika Kulik, & Allan L. Goldstein	Thymosin β 4 and the fibrotic switch
Marie-Christine Pardon et al.	Protective effects of thymosin β 4 in the ageing brain following lipopolysaccharides-induced systemic inflammation
PLENARY SESSION III: Thymosin α1 – mechanism of action, preclinical and clinical trials in COVID-19, and studies in depression	
Penghui Zhou et al.	Thymosin α 1 protected cells from excessive activation in severe COVID-19
Eleftherios Mylonakis et al.	Effect of thymosin α 1 on reversing lymphocytopenia among patients with hypoxemia and lymphocytopenia due to COVID-19 infection
Claudia Matteucci et al.	Unravelling the pleiotropic effect of thymosin α 1: From the experience to the identification of novel mechanisms of action
Ahmed Awad, William B. Ershler, Mary Parrigon, & Cynthia W. Tuthill	A pilot trial of thymosin α 1 to prevent COVID-19 infection in renal dialysis patients
Hemmo A. Drexhage et al.	Thymosin α 1 treatment to correct the reduced numbers of naïve CD4+ cells and the low-grade inflammation in patients with major depression
Antonella Minutolo et al.	Thymosin α 1 mitigates cytokine storm: Quenching the fire in COVID-19 patients
October 22, 2022	
PLENARY SESSION IV: Thymic extracts and peptides, mechanism of action, clinical trials in hepatitis B, infectious diseases and cancer	
Yiting Wei & Lixin Wang	Thymosin α 1 reverses polarization of efferocytotic M2-tumor-associated macrophages via a lysosomal TL4-SHIP1 cascade
Joanna Izabela Lachowicz et al.	Metal-driven biochemistry of thymosin β 4
Bing-liang Lin et al.	Safety and efficacy of thymosin α 1 in the treatment of hepatitis B virus-related acute-on-chronic liver failure: A randomized controlled trial
Hui Liu et al.	Hypofractionated radiotherapy combined with weekly chemotherapy in patients with unresectable or recurrent thymic epithelial tumor: A prospective, single-arm phase II study (GASTO-1042)
Javier Paino et al.	The use of silver nanoparticles as an efficient delivery system for human umbilical cord mesenchymal stem cells growth factors. Building a cell regeneration environment for burned patients
Jolanta Artym, Michał Zimecki & Aleksander Skotnicki	An overview on immunological activity of calf thymus extract TFX® and its therapeutic benefits
PLENARY SESSION V: Thymosin peptides and prothymosin, mechanism of action, secondary HLH, atherosclerosis, and combination chemotherapy in treating medulloblastoma cancer	
Christian Kupatt-Jeremias	Angiogenic potential of MRTF-A, a downstream signal of thymosin β 4, in ischemic pig muscles

Sonali Munshaw, Andia N. Redpath, Benjamin Pike, & Nicola Smart	Thymosin β 4 preserves vascular smooth muscle cell phenotype in atherosclerosis via regulation of low density lipoprotein receptor related protein 2 (LRP1)
Adan Rios, Frances Cervoni-Curet, & Binoy Yohannan	Secondary hemophagocytic lymphohistiocytosis (HLH): Five years experience at the unhealth McGovern Medical School at Houston, Texas
Jianguo Sun et al.	Comparison of efficacy and safety between EGFR-TKI combined with thymosin and EGFR-TKI monotherapy in advanced NSCLC with active EGFR mutations
Aisha Naeem, Maria Laura Avantaggiati, Olga Rodriguez, Chris Albanese	Thymosin β 4 enhances sensitivity of human medulloblastoma cells expressing high protein levels of p53 to first-line chemotherapeutics

References

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