



Reprint
from issue 3 / 2008

Synthetic Thymic Peptides in the Restoration and Modulation of Immune Response

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Drug monitoring studies in chronically seriously ill patients show pronounced clinically positive effects and a rapid improvement in the immune system condition

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Chronic diseases and, in particular, tumourigenic illnesses as well, are axiomatically attended by a false regulation of the immune response. Due to the complexity of our immune system and the numerous regulatory functions for stimulation or suppression of immune functions, the opportunities for false regulation, and with it, dysfunctional immune response, are very diverse.

The thymus gland has a decisive role as the primary organ for the selection of immune competent cells and, thereby, in the co-ordination of the immune response. It is jointly responsible in this, with its positive and negative selection of immune competent cells, instrumental for the function of the cellular immune response.

The thymocytes are specifically activated, through their T cell receptors and MHC contact, by the numerous antigen-presenting cells (dendrites, macrophages, B cells) present in the medulla of the thymus gland.

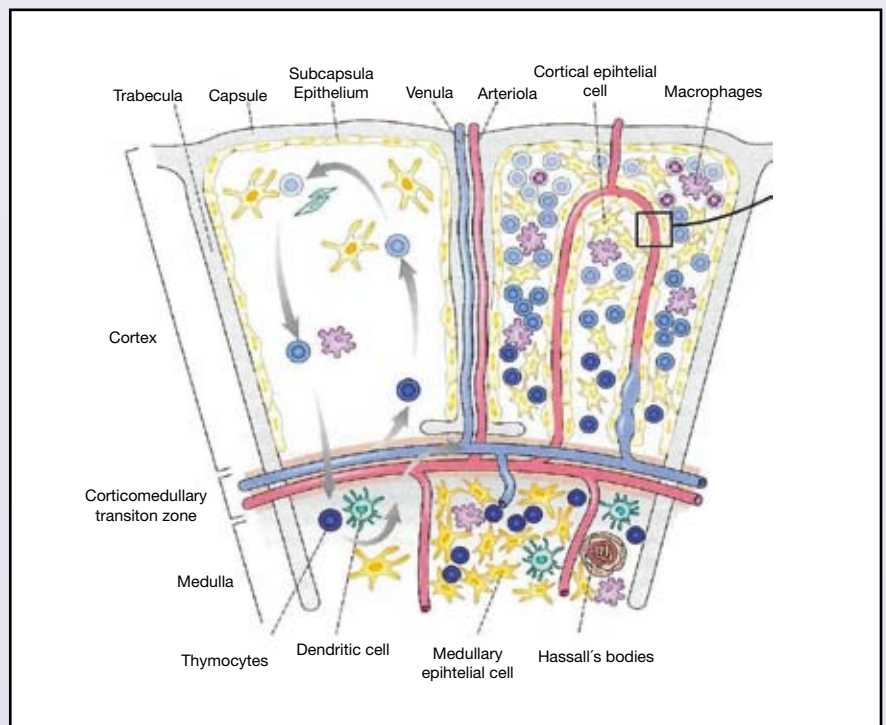


Fig. 2: Schematic depiction of the organization of the thymus

Holländer: Immunologie – Grundlagen für Klinik und Praxis, Elsevier 2006

Too strong or too weak an activation leads to the cell death of the thymocytes. Thymocytes with an average affinity at their TCRs for the MHC binding site of the anti-

gen presenting cells leave the thymus gland as functioning T cells.

Stimulated by thymic peptides, in particular thymopoetine and thy-

mosine, they develop into effector-cells and are then responsible for the specific cellular immune response. Thereby, the thymic peptides also stimulate the cytokines, such as IL-2, necessary for the stimulation of the effector-cells.

Thymocytes with a somewhat stronger affinity develop under the influence of thymulin into natural T regulators (CD4/CD25/Fox P3+) and have a marginally immunosuppressive effect.

immune response and also distinct disruption to thymus functions can be shown in these diseases, therapeutic modulation with thymic hormones and peptides is the basis for the successful treatment of chronic illnesses as well as tumourigenic diseases.

Numerous effects on the immune system, then, are postulated for thymic peptide therapy. In principle, thymic peptides, if they include the agents responsible for immune

also of counter balancing particular dysfunctions, such as suppression and escape mechanisms, and therefore of influencing, e.g. in tumourigenic diseases, deficits in effector-cells such as cytotoxic lymphocytes and NK cells.

They can regulate down the T8 and T4 regulatory cells, responsible for the suppression of effector-cells, and accordingly regulate up cytotoxic and killer cells necessary e.g. for tumour response.

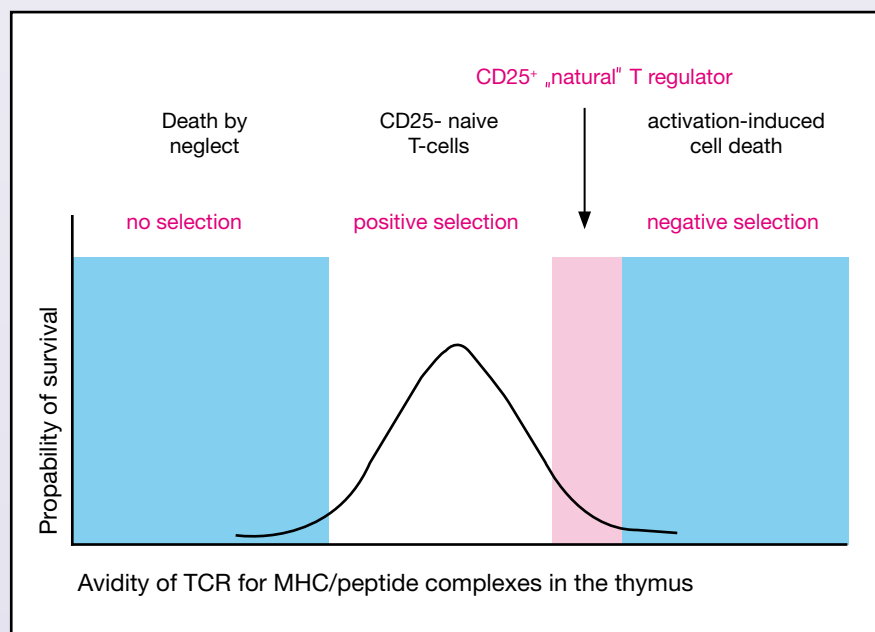


Fig. 3: Schütt, Bröker: *Grundwissen Immunologie*, Elsevier 2006

A functioning thymus gland, with its numerous thymic hormones and thymic peptides, responsible for the regulation of the immune system, is for this reason the basis for the successful treatment of diseases of the immune system.

Since very nearly all acute on chronic illnesses, in particular, however, tumourigenic diseases, are associated with dysfunction of the cellular

system regulation, are suited, in a complex manner, to the restoration almost all immune functions. In this, the effect rests predominantly in the modulation by deficient thymic function of accrued pathogenic dysfunctions of the immune processes.

Thymic peptides, via the modulation of the regulation of immune defences, are especially capable

By modulating the regulatory cells, however, excessive reactions induced by the deficient function of regulatory cells can be beneficially influenced in autoaggressive illnesses as well. In particular, therefore, the goal of a differentiated thymic peptide therapy is modulation and, as a consequence, the suppression or stimulation of abnormal immune functions under adequate monitoring by immune phenotyping.

For a short while, synthetic thymic peptides (active agent GKL-03, preparation Thymrevit®, Vita-Cos-Med Klett-Loch GmbH, Mannheim) have been available for such immunomodulation.

These are part of a chemically identical, entirely synthetic thymus gland extract of the short-chain tetrapeptides typically found in the thymus gland. The extract contains the complete library of thymic peptides of low molecular weight.

The peptides are prepared from biochemical amino acids. In a drug monitoring study of 45 patients, the possibility of a modulation of immunological functions was investigated using measurement of cellular immune functions.

Thymus Peptide	mol. wt. [D]	Cellular Defence	Cytokine	Neuroendocrine System
Homeostatic Thymus Hormone (HTH α , HTH β)	15,000 16,000	Compensates immunodeficiency; has radioprotective properties	n.k.	is influenced
Prothymosin α (pro T α)	12,000	Activation of NK and LAK cells; adhesion of Ly and Mo to tumour cells; LPR on PHA	IL- 1 β \uparrow ; IL- 2 \uparrow ; IFN- γ \uparrow ; TNF- α \uparrow PGE2 \downarrow	n.k.
Thymopoietin II	5,600	Maturation of prothymocytes into thymocytes; stimulates T helper cells	n.k.	n.k.
Thymosin β 4 (T β 4)	5,000	Activates phagocytosis of Mo, inhibits free radicals and arachidonic acid metabolites (PGF1 α , Tx β 2)	IL-1 \downarrow , IL-6 \downarrow , TNF- α \downarrow , PAF \downarrow	LH \uparrow , LH-RH \uparrow , PRL \uparrow , GH \uparrow
Thymic Humoral Factor (THF)	3,400	Stimulates intrathymic maturation of lymphoid cells	IL- 2 \uparrow , IFN- α \uparrow , CSF \uparrow , MIF \uparrow	n.k.
Thymosin α 1 (T α 1)	3,100	Maturation and differentiation of thymocytes (CD 4+CD 8+); Activation of CD 2+ cells; antagonist to steroid-induced Ly apoptose; inhibition of NSCLC tumour cell-growth	IL- 2 \uparrow , IFN- α \uparrow , IFN- γ \uparrow , MIF	TSH \downarrow , ACTH \downarrow , PRL \downarrow
Thymosin α 7 (T α 7)	2,500	Activates T suppressor cells	n.k.	n.k.
Thymulin (FTS- Zn)	1,000	Differentiation of prothymocytes; activation of NK, CTL and T helper cells; induction of IgA; -G, -E; DTH \uparrow	IL- 2 \uparrow , CSF \uparrow , CAMP \uparrow , PG	GH \uparrow , PRL \uparrow , TSH \uparrow , LH \uparrow
Thymopentine pentapeptide (TP5)	680	Inhibition of T suppressor cells	n.k.	ACTH \uparrow , β -Endorphin \uparrow β -Lipotrophin \uparrow

Fig. 4: Immunological and Neuroendocrine Effect of Thymic Peptides
E. D. Hager: Komplementäre Onkologie, Forum Medizin 1996

For this, patients were selected who used no other additional therapy over the observation period of four weeks or who were in a stabilised immune condition and were being treated long-term under the same regime without affecting their immune functions.

Four patients were examined at a specialist oncological clinic during or post chemotherapy with regard to the effect on the immunological functions after or during chemotherapy under treatment with the medication and their clinical condition evaluated.

Moreover, the clinical effect on the disease, state of health and tolerance was observed. Additionally, the question as to the occurrence of side effects on oral administration of the thymic peptides was fundamental.

As a rule, the patients were observed for four weeks. As a part of this, immunophenotyping was performed before any treatment with the synthetic thymic peptides was given, then after 14 days and at four weeks. Above all else, the behaviour of the CD4+ / CD25+ regulatory T-cells, lymphocytes, T3- lymphocytes, NK cells and cytotoxic cells was assessed.

Some selected patients were treated for several months with synthetic thymic peptides and observed. For these patients, additional immunophenotyping was carried out at more frequent intervals.

The dosage was a uniform 10 mg per day. The capsules with the active agent GKL-03 were taken each time with a glass of water, half an hour before breakfast.

The following disease patterns were treated:

Ca. Breast	17
Ca. Prostate	9
Bronchial/Lung Ca.	3
Intestinal Ca.	2
Ovarian Ca.	1
Ca. Appendix	1
Liposarcoma	1
Lymphoma	1
Haemangioblastoma	1
Myelodysplastic Syndrome	1
Muscular and Neurological diseases	2
Immune deficiency	2
Colitis	1
Rheumatism	1
Borreliosis	1
Endogenous Eczema	1
→ Observed Patients	45

Fig. 5: Disease Patterns Treated

Positive immunological effects	39 (92,86 %)
Deficient immunological effects	3 (7,14 %)
Discontinued due to lack of compliance	3

Fig. 6: Percentage Evaluation of Immunologically Positive Effects

Significantly, no patients complained of any side effects. 80 % of the patients reported that on taking the drug they felt distinctly better, about 13 % indicated that they felt especially well while taking the drug, 7 % discontinued the treatment on various grounds.

Since chronic diseases and tumorigenic diseases are predominantly involved, the good state of health and the improvement in capability indicated by most patients are already noticeable. None of the patients suffered a noticeable deterioration in their clinical condition.

Of the patients without macroscopic tumorous masses, none suffered a relapse or the formation of metastases during the observation period or post observation.

In the tumour patients with macroscopically detectable tumorous masses and advanced metastatic dispersal, it was startling that the condition under continuous che-

motherapy or radiochemotherapy was markedly positively affected in particular (four patients treated at Dr. Stein's oncology clinic, four patients from Dr. Briken's practice).

Just as impressive was that therapeutically induced lymphopenias and T3 lymphocyte deficits measurably improved in most cases in the brief observation period of four weeks. The initial effect here was most pronounced within 14 days. Since a marked lymphocytopenia of itself already suggests a significant immunodeficiency, this effect should be particularly emphasised.

In a greater proportion of the patients there was early a noticeable regulation of the CD4/CD25 characterised T cells towards normal values (28 patients). This is particularly remarkable, since these cells are therapeutically difficult to regulate in the short term.

In 23 patients, the regulation of the CD4/25 T regulators was linked to a reaction of the lymphocytes, T3 lymphocytes and in part also of the effector-cells in the sense of an increase or to an overreaction in the sense of a decrease.

Since normal values for the complexity of immunological processes cannot be determined, the short-term beneficial effects of regulation must be viewed as a good opportunity for immune modulation of diagnosed immune disorders.

However, it should be noted that, after varying periods during the course, particularly, after the marked initial effect, there occurred an adaptation.

According to current research, the chemical agent GKL-03 is suited to act beneficially on the regulation of immunological functions in particular, in immunosuppressive immune conditions, noticeably to improve mature lymphocytopenias and, through its effect on the T-regulatory cells, to stimulate effector-cells, particularly cytotoxic lymphocytes and NK cells.

Particular emphasis should be placed on the high tolerance to the drug. There are very nearly no side effects. Clinically, almost all patients felt better while under treatment; in some cases there was a distinct improvement in the overall picture and an improved capability, despite serious tumourigenic disease (particularly as well, in the patients treated at Dr. Stein's oncology clinic).

One patient with metastasising carcinoma of the prostate (multiple bone metastasis), which, after unsuccessful hormone therapy and non-compliance with chemotherapy, defeated every further classic medical treatment, was treated for 15 months with GKL-03 as a long-term observation, from October 2006 until January 2008.

Despite a steadily rising PSA, the patient is doing excellently with fully preserved capability and continuing absence of symptoms. Therapeutically, he was being treated additionally with Zometa and vitamin infusions during the regulation treatments.

Here could be shown very well the effect of regulating down the CD4+/CD25+ cells with an analogous rise in NK cells (Fig. 7).

Ca. Prostate

1 cap. GKL-03 daily; B., G., 16 June 31

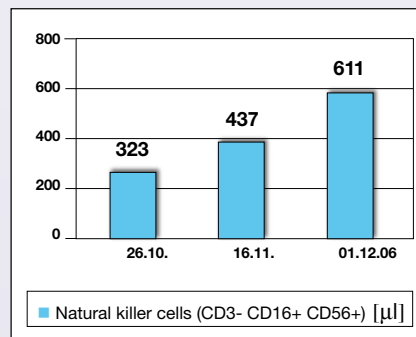
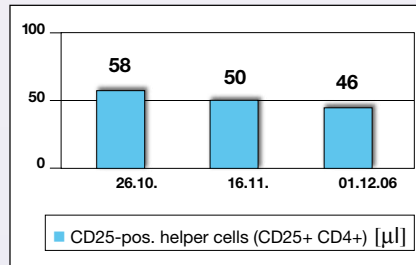


Fig. 7 Ca. Prostate (with extensive bone metastasis, without further invasive therapy) Distinct improvement in the NK cells, regression of CD25+/ CD4+ regulatory T- Cells

Particular emphasis should also be placed on the stabilisation or, in fact, stimulation of the lymphocytes and T3 lymphocytes under continuous aggressive chemotherapy with simultaneous distinct clinical effect.

Without continuous chemotherapeutic or radiotherapeutic measures, the lymphocytopenia and the respective T3 and effector deficiencies, commonly of long duration, were rapidly improved (Fig. 8, fig. 9), apart from where this is a consequence of aggressive therapy.

At the same time, almost all patients also show clinically positive

progress in the post-observation phase. It is known from the Literature that survival time and prognosis are closely linked to the individual's immune condition.

Ca. Prostate

1 cap. GKL-03 daily; Th., M., 19 Dec. 39

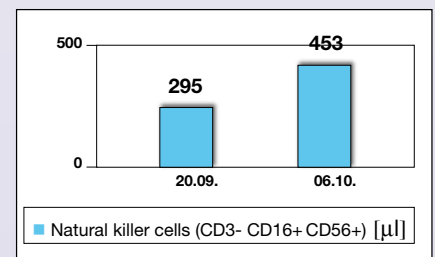
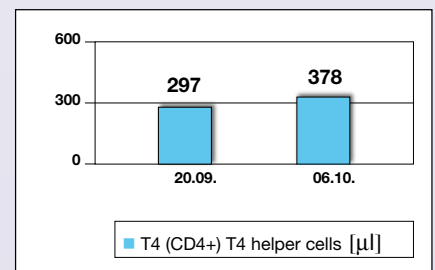
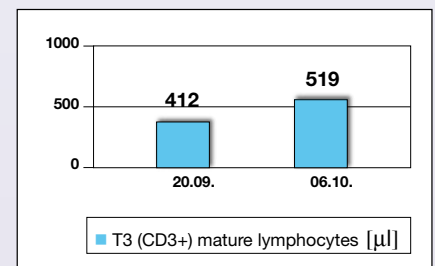
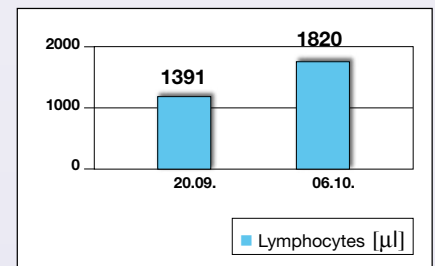


Fig. 8 Ca. Prostate (with extensive local recurrence). Distinct improvement in lymphocytes, mature T lymphocytes (CD3+), T4 helper cells (CD4+), Natural killer cells (CD3- CD16+ CD56+)

Ca. Breast

1 cap. GKL-03 daily; R, B., 29 April 60

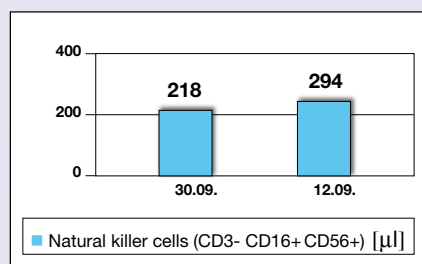
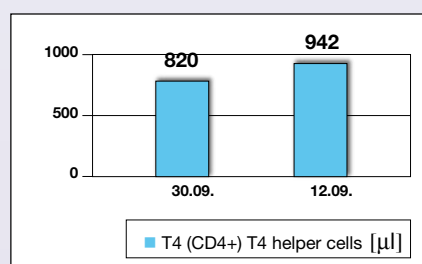
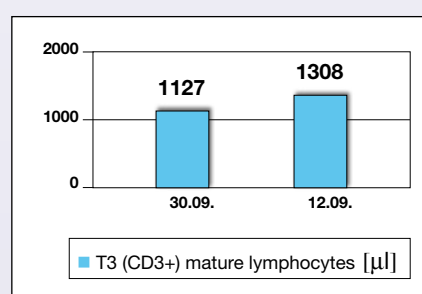
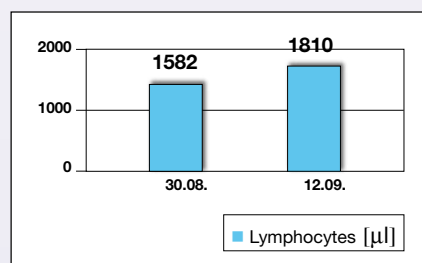


Fig. 9: Ca. Breast (without further therapy). Distinct improvement in lymphocytes, mature T lymphocytes (CD3+), T4 helper cells (CD4+), Natural killer cells (CD3- CD16+ CD56+)

In the patients with autoaggressive or generally with immunodeficiency-linked diseases, there was a marked regulation of the CD4+ / CD25+ regulatory cells with a reduction in

infection lability and symptomatic improvement (e.g. in colitis ulcerosa).

Assessment of the clinical effect was not possible for the patients with muscular and neurological diseases, due to the brevity of the treatment period. There was, however, here in both observed patients likewise an appreciable regulatory effect on CD4+ / CD25+ T-lymphocytes (see Fig. 10).

CD4 / CD25 helper cells

1 cap. GKL-03 daily; Sch., U., 30 March 53

In a treated borreliosis there was a distinct reduction in inflammation activity and improvement in the clinical picture.

Summary:

With synthetic thymic peptides (chemical agent GKL-03 - Thymovit® preparation), there is now a demonstrably potent immunomodulator, effective in the short term,

for numerous diseases linked to immune dysfunctions.

The preparation is suited to elicit modulation or stimulation, in particular for the treatment of immunodeficiencies in oncological diseases.

As well, other diseases of a degenerative or autoaggressive nature linked to disruptions to immune functions have responded well to the drug.

It is free of side effects and leads, where well tolerated, to a temporary improvement in the general state of health as well as in capability.

The great benefit is the option of oral administration. Apart from this, there is no risk of BSE, since it is a question of an entirely synthetic preparation, manufactured from bi-chemically obtained amino acid.

Literature with the author

Authors:

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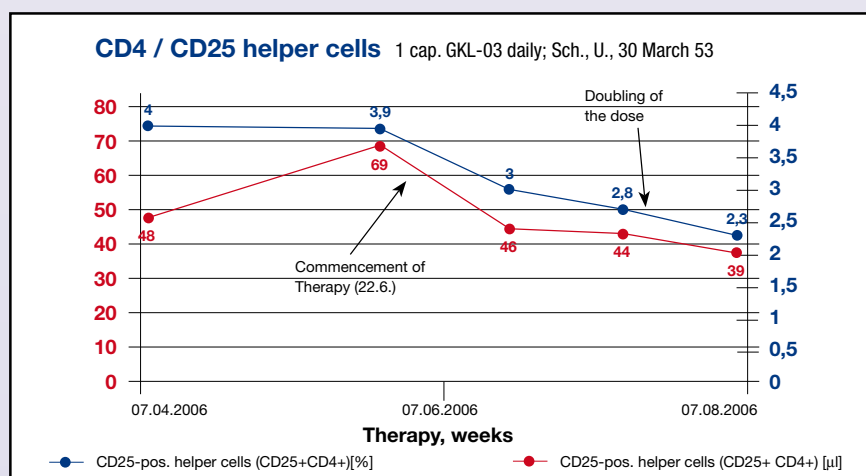


Fig. 10: Bulbar Amyotrophic Lateral Sclerosis. Here, there was a consistent regression of the CD4+ / CD25+ regulatory cells in four individual measurements as parameters for a decidedly beneficial effect on the excessive inflammation reaction

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Revitalisation • Immune restoration • Immune enhancement



The thymus gland is the most important monitoring and control organ in the body's immune system. Degeneration of the organ or damage to it, which is linked to advancing age or severe illnesses, leads to many secondary diseases. Chronic diseases are particularly linked to a so-called immunodeficiency (weakness of the immune system). Cancer and acquired immune deficiencies lead to an impairment of the functions of the thymus gland.

The synthetic, chemically identical thymic peptides contained in the active ingredient, GKL03, induce the modulation or regulation of important immune processes when administered orally. Experience and studies demonstrably indicate that even with severe immune disorders, an improvement of the immune situation and thus an amelioration of the disease itself can be achieved with thymic peptides.

Areas of application:

For the dietary treatment of diseases connected with immune disorders and immune deficiencies, particularly cancer and severe infections as well as for immune restoration after chemotherapy, operative interventions and radiation.

**Thymrevit® revitalisation capsules
10 mg und 1 mg**

**Dietary product for specific
medical purposes
(supplementing a balanced diet)**

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