UDK 578.27+615.32

THE GMP-BASED DRUG SUBSTANCE SCTL DEVELOPMENT AIMING AT PREVENTION OF OPPORTUNISTIC INFECTIONS AFTER X-RAY- AND CHEMOTHERAPY OF CANCER. A SYNTHETIC COMBINATORIAL TETRAPEPTIDE LIBRARY SUBSTITUTION FOR CALF THYMUS EXTRACT

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Received 23.05.2013

SCTL is the fully synthetic correlate of an enzymatic partially hydrolyzed extract from calf thymus. To exclude completely the transmission of bovine spongiformic encephalitis by the bovine thymus product a fully synthetic correlate of the active principles in the thymus tissue hydrolysate has been developed, namely SCTL. This synthetic peptide library has meanwhile substituted calf thymus extract preparations in several cosmetics and drug products. The active principles of SCTL have been invented by the author but the application of the drug substance in cosmetic and pharmaceutical products has been exploited by others. For SCTL only limited pharmacological and toxicological data are available. Some interesting biological activities, though, have been shown for SCTL which might explain to some extend the modes of action and its clinical effectiveness.

Key words: synthetic correlate of an enzymatic partially hydrolyzed extract from calf thymus.

SCTL is the fully synthetic correlate of an enzymatic partially hydrolyzed extract from calf thymus, HTX. To exclude completely the transmission of bovine spongiformic encephalitis (BSE) by the bovine thymus product a fully synthetic correlate of the active principles in the thymus tissue hydrolysate has been developed, namely SCTL. This synthetic peptide library has meanwhile substituted calf thymus extract preparations in several cosmetics and drug products.

The active principles of SCTL have been invented by the author but the application of the drug substance in cosmetic and pharmaceutical products has been exploited by others. For SCTL only limited pharmacological and toxicological data are available. Some interesting biological activities, though, have been shown for SCTL [Birr et al., 1987, 1998, 2003] which might explain to some extend the modes of action and its clinical effectiveness.

In traditional European medicine the application calf thymus extract preparations in geriatric and immunodeficiency diseases has been practised for more than three centuries. In several countries traditional drug preparations and cosmetics from HTX have been used successfully. There are field reports on prevention of alopecia, opportunistic infections and cancer. Several publications report about the efficacy of the product in the reduction of hair loss secondary to cytostatic chemotherapy.

But the mode of action of HTX , the partially hydrolyzed extract from calf thymus, is not known. Since biological effects on the pro-

*)With appreciation dedicated to Professor Serhiy V. Komisarenko, Palladin Institute of Biochemistry, Kyiv, Ukraine, on the occasion of his 70th birthday, July 9, 2013.

liferation of human lymphocytes have been shown, actions similar to other thymus proteins are assumed. Precise descriptions of the mode of action are hampered by the fact that drug products from HTX are by no means consistent in preparation and composition.

In the effort to completely prevent the transmission of BSE by this kind of product a fully synthetic peptide library SCTL was developed which resembles the major components of HTX in its chemical composition. SCTL contains di-, tri-, tetrapeptides and free amino acids, all in number and quantity specific for calf thymus partial hydrolysates. The preparative consistency and chemical composition of this well-defined synthetic drug product will be described in more detail in the next section of this article.

Chemistry of SCTL

Background

The European bovine & transmissible spongiformic encephalitis (BSE / TSE) catastrophe of the recent decades has put this entire field of natural bovine extract therapeutics into crisis. Many thymus preparations have become banned by law. Since then, a very well established clientele among the elderly, but also patients, therapists, pharmacies and industries were looking for safe alternatives for many of these well established bovine tissue extract drug products.

One of these products was HTX from bovine starting material. The risk of BSE/TSE transmission could not be fully excluded. Even if the traditional manufacturing process was carried out thoroughly, due to the complex composition (amino acids, peptides, saccharides, fats etc.) and the naturally occurring variability in the primary tissue source, an undesirable inconsistency in the product properties was observed. Due to the lack of a specific chemical marker, it was not possible to compensate this by standardising the product at the end of the manufacturing process. Owing to the manufacturing process varying by-products from thymus tissue, which were considered to be impurities remained in the finished. It was not possible to separate these from the target fraction of the enzymatic hydrolysate.

A major research & development project was launched at the author's laboratory by an industry sponsor to find a composition which has similar pharmacological properties and is comparable to the main fraction of the partial enzymatic hydroly-sate HTX. In order to achieve the closest synthetic version, analytical investigations were carried out with emphasis on the peptide composition of this natural tissue extract. The aim of these studies was the development of a fully synthetic chemically standardized product resembling as close as possible the chemical composition and the immune-pharmacological properties of HTX.

The main fraction of HTX has an 80% protein content and a molecular weight range of up to 10 kDa. It was determined that one third of the natural material contains free amino acids together with short oligo peptides, which by pool sequence analysis were determined to consist mainly of tetrapeptides accompanied by traces of di- and tripeptides. Furthermore, there were some other natural compounds like hexoses, saccharides, sialic and nucleic acids, also modifications of the peptide compositions were detected.

Based on these results it was considered to synthesize a statistic combinatorial peptide library composed out of di-, tri- and tetrapeptides and a pool of free amino acids, in number and molar proportional quantity similar to the amino acid composition of

the main fraction of HTX, without adding any further ingredient. Following this way SCTL has been developed as a synthetic version of the peptide content in natural thymus partial hydrolysate, conceptually differing from the development of molecularly defined thymic polypeptides [Birr et.al., 1979, 1983, 1984].

Analytical Investigations

Due to the inconsistency in the composition of HTX several batches of the natural product were analysed for obtaining reliable mean values.

The sequencing of the terminal amino acids of the main fraction of HTX resulted in a termination after three cycles, leading to the conclusion that the natural hydrolysate consists mainly of free amino acids as well as di-, tri- and tetrapeptides. The sequencing also showed that these peptides consist of a statistical distribution of homologues which could not be further separated for component identification.

The analytical data show that HTX consists of approximately 32.5% free amino acids, the remaining are di-, tri- and tetrapeptides. The peptides consist mainly of Asp, Glu, Pro, Gly, Ala, Val, Leu, Lys and Arg, whereas the absence of Cys in the peptides may result from oxidative destruction during analysis .

The lipid amount was about 8% and the amount of nucleic acids less than 0.1%.

The amount of other compounds found were 8% hexoses, up to 1.5% sialic acid and

about 5% mono saccharides. These compounds of HTX were considered as carrier agents or impurities and consequently not included in the peptide synthesis concept for the generation of SCTL.

Analytical comparison of the natural HTX with synthetic SCTL by amino acids analysis and RP-HPLC

A comparison of free and total amino acids is given in Table 1 to Table 3.

The HPLC analysis of synthetic SCTL and the main fraction of the partial hydrolysate of calf thymus HTX show a similar profile as demonstrated in Fig. 1 and Fig. 2.

From these findings it was decided to synthesize a statistic combinatorial peptide library consisting mainly of tetrapeptides and amino acids together with amounts of up to 10% di- and tripeptides each. The pool of amino acids was standardised with regard to the unprotected amino acids in each reaction step.

Studies for determination of the biological activity by mitogen costimulation of separated HTX by-product fractions gave no evidence, that these portions of HTX have any immunological action. Therefore, these were considered to be impurities not required in the composition of the synthetic version.

The synthetic chemical product SCTL has no risk for BSE/TSE transmission as could be the case for natural HTX due to the route of manufacturing of the natural product from bovine thymus tissue. Moreover, the synthetic SCTL does not contain impurities like nuleic acids, sugars and fats, as it is caused for the natural product HTX through its route of manufacture from thymus tissue.

Table 1. **Free amino acids determination in HTX and in SCTL for comparison**

Batch	8863 (1)	8863 (2)	968	T.E.P.	Mean HTX	Theor. SCTL
Amino acid	**[% w/w]**	**[% w/w]**	**[% w/w]**	**[% w/w]**	**[% w/w]**	**[% w/w]**
Asp	2.09	2.15	2.23	3.21	2.42	2.40
Thr	5.70	5.69	4.48	4.67	5.13	9.24[a)]
Ser	3.84	3.82	5.48	4.53	4.42	8.60[a)]
Glu	8.60	8.32	9.78	8.39	8.77	6.47
Pro	3.10	3.11	2.33	3.06	2.90	2.29
Gly	2.77	2.60	2.94	2.98	2.82	4.93
Ala	8.57	8.43	7.88	8.42	8.32	11.67
Cys	–	–	–	–	–	0.61
Val	5.63	5.69	6.3	8.00	6.40	6.74
Met	2.46	2.52	3.23	5.38	3.40	3.23
Ile	4.62	4.41	5.57	5.93	5.13	4.24
Leu	14.74	14.91	14.45	15.87	14.99	14.12
Tyr	4.89	4.41	5.34	1.30	3.99	0.36
Phe	5.56	5.83	5.71	6.36	5.87	4.26
Trp	–	–	–	–	–	0.00
His	1.32	1.30	–	–	0.65	1.22
Lys	12.78	13.24	12.61	11.00	12.41	10.35
Arg	13.32	13.58	11.67	10.91	12.37	9.27
Total	100	100	100	100	100	100

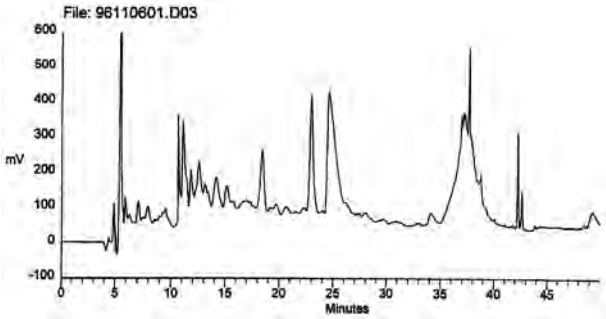


Fig. 1. **RP-HPLC Analysis of synthetic SCTL (batch SP-01)**

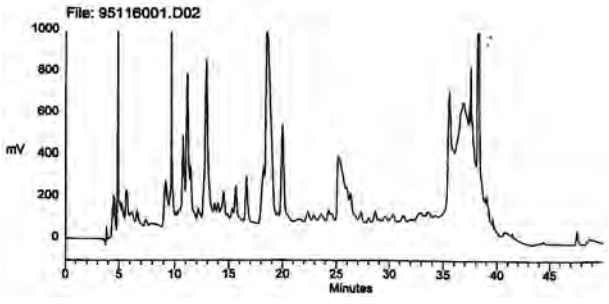


Fig. 2. **RP-HPLC Analysis of natural HTX Reference**

Table 2. **Total amino acid composition in HTX and in SCTL for comparison**

Batch	8863 (1)	8863 (2)	968	T.E.P.	Mean HTX	Theor. SCTL
Amino acid	**[% w/w]**	**[% w/w]**	**[% w/w]**	**[% w/w]**	**[% w/w]**	**[% w/w]**
Asp	8.87	9.20	9.77	7.60	8.86	6.05
Thr	2.83	3.18	3.42	5.19	3.65	3.55
Ser	1.32	1.81	1.85	5.29	2.57	3.30
Glu	14.87	14.94	15.51	14.68	15.00	8.36a)
Pro	6.12	6.01	5.71	7.52	6.34	10.23a)
Gly	10.10	9.47	8.91	10.11	9.65	24.74a)
Ala	8.69	8.40	7.36	7.75	8.05	11.70
Cys	0.00	0.00	0.00	0.58	0.14	0.23
Val	6.44	6.57	6.22	6.28	6.38	6.15
Met	1.44	1.37	1.81	2.56	1.80	1.24
Ile	4.21	4.26	4.63	4.24	4.33	3.53
Leu	8.55	8.67	8.85	7.67	8.44	5.52
Tyr	0.48	0.39	0.91	0.00	0.44	0.14
Phe	3.64	3.60	4.05	3.66	3.74	2.07
Trp	0.00	0.00		0	0.00	0.00
His	1.13	1.08	1.04	0.43	0.92	0.47
Lys	11.90	11.34	11.07	8.49	10.70	6.94
Arg	9.41	9.70	8.89	7.96	8.99	5.77
Total	100	100	100	100	100	100

Table 3. **Free and total amino acid differentiation in HTX and SCTL for determination of the peptide contribution**

Batch	Mean HTX free AA	Mean SCTL free AA	Mean HTX total AA	Mean SCTL total AA	Δ HTX vs. SCTL free AA	Δ HTX vs. SCTL total AA
AA	**[% w/w]**	**[% w/w]**	**[% w/w]**	**[% w/w]**	**[% w/w]**	**[% w/w]**
Asp	2.42	3,11	8,86	6,18	−0,69	2,68
Thr	5.13	6.97[d)]	3,65	2,86	−1,84	0.80
Ser	4.42	5.06[d)]	2,57	2,09	−0,64	0.47
Glu	8.77	6.87	15.00	8,60	1.90	6.40
Pro	2.90	2.67	6.34	8.12[c)]	0.23	−1.78
Gly	2.82	5.60	9.65	33.45[c)]	−2.78	−23.81
Ala	8.32	11.55	8.05	11.21[c)]	−3.22	−3.16
Cys[a)]	0.00	0.05	0.14	0.09	−0.05	0.06
Val	6.40	7.24	6.38	4.88	−0.84	1.50
Met	3.40	3.51	1.80	0.44	−0.11	1.36
Ile	5.13	5.10	4.33	2.91	0.03	1.43
Leu	14.99	15.06	8.44	5.42	−0.07	3.02
Tyr	3.99[b)]	0.13	0.44	0.01	3.85	0.43
Phe	5.87	4.83	3.74	1.98	1.04	1.76
Trp	0.00	0.00	0.00	0.00	0.00	0.00
His	0.65	0.88	0.92	0.20	−0.22	0.72
Lys	12.41	11.40	10.70	6.98	1.01	3.72
Arg	12.37	9.98	8.99	4.59	2.39	4.40
Total	100.00	100.00	100.00	100.00	°	°

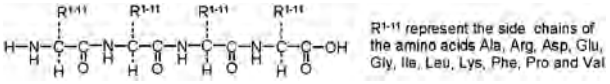
[a)] Destroyed by analysis conditions; [b)] Only 10 % value specified [c)] Surplus for compensation of 0.5 % collagen (Pro, Gly, Ala) in total composition; [d)] Surplus for thermal destruction compensation in total composition.

The Synthetic Combinatorial Thymus Tetrapeptide Library SCTL

The novel drug substance SCTL is a synthetic version of the former natural thymus partial hydrolysate HTX, originally prepared by enzymatic processing from calf thymus tissue. SCTL, mimicking the complex structure of the natural HTX, by synthetic means is composed of amino acids, di-, tri- and tetrapeptides in quantities and nature resembling the composition of partially hydrolyzed thymus tissue.

The drug substance SCTL is a synthetic statistical combinatorial thymus tetrapeptide library composed of:

a) Linear di-, tri- and tetrapeptides containing the residues R1-11 of the natural L-amino acids Alanine, Arginine, Aspartate, Glutamate, Glycine, Isoleucine, Leucine, Lysine, Phenylalanine, Proline and Valine in a statistical combination



and

b) the 17 natural L-amino acids or their HCl salts, respectively: Ala, Asp, Arg×HCl, Cys(H_2O)×HCl, Glu, Gly, His(H_2O)×HCl, Ile, Leu, Lys×HCl, Met, Phe, Pro, Ser, Thr, Tyr and Val.

The Peptide Library SCTL

The synthetic drug substance SCTL is chemically manufactured from and consists only of the naturally occurring L-amino acids, either as free amino acids or as their statistical synthetic combinations in di-, tri- and tetrapeptides and their salts, respectively. These kinds of products are called combinatorial peptide libraries containing the individual amino acids and peptides in all statistically possible combinations. Because of the similarity of the individual components, the molecular quantities in traces of individual peptides in the library cannot be separated from each other and therefore cannot be determined individually. Only the statistical combination of all peptides in the library as a whole can be described and analysed. Therefore, the product SCTL for pharmaceutical development is considered a mono compound drug substance.

The molecular formula given above resembles the statistical combinatorial peptide library of different di-, tri- and tetrapeptides as well as free amino acids. The relative molecular masses have a range from 75 to 643, due to the content of Gly as lowest to a tetrapeptide consisting of $(Arg)_4$ as a maximum. SCTL is an off-white powder, which was manufactured at ORPEGEN, Germany [Birr et al., 1998].

The GMP-based carefully standardized manufacturing process is a six steps operation. In the first, third and fifth step carboxyl protected amino acids, di- and tripeptides, respectively, are coupled with N-protected amino acid derivatives. It was intended to synthesize a synthetic combinatorial peptide library containing trace amounts of monomers, di-, tri- and tetrapeptides similar to the low molecular weight fraction of a partial hydrolysate of calf thymus HTX. This is achieved by the limit of detection (≤ 2%) of the photometric quantitative Ninhydrine method used as an in process control, IPC, carried out during each synthesis cycle of the manufacture. In the second and fourth step the terminal N-protecting groups are removed. In the final step the free peptides are obtained by catalytic hydrogenation of all remaining benzyl type protecting groups.

In all operations, the reactive side groups of those amino acids containing side functions are protected by Z- or OBzl groups, benzyl esters and (Z) benzyloxycarbonyl protection groups, respectively. Some of the protected amino acids are used as salts due to their better solubility and stability. All functional side chains of the natural L-amino acids remain protected during the synthesis up to the last step 6, where they are then deprotected simultaneously together with the N- and C-terminal protecting groups.

The absence of traces from benzyl-type protecting groups was proven by 300 MHz ^{1}H-NMR spectroscopy in seven final drug substance batches of SCTL.

Also by capillary electrophoresis, CE, in a batch-to-batch consistency documentation the synthetic molecular identity of seven dif-

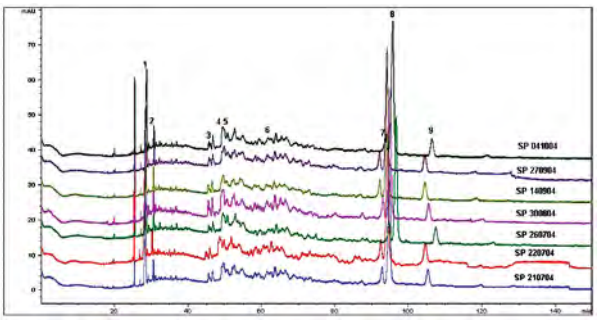


Fig. 3. **Batch-to-batch consistency documentation by CE (Capillary Electrophoresis) on seven charges of SCTL manufactured under GMP restrictions**

ferent batches of the combinatorial tetrapeptide library was demonstrated as shown in figure 3.

Assay for the biological standardisation of GMP-manufactured SCTL batches

Mast cells contain the serine proteases tryptase and trypsin. Keratinocytes of human skin dispose receptors which are activated by serine proteases leading to changes in cell function which are not yet fully recognized and understood. In our search for an *in-vitro* assay suitable for the biochemically standardized manufacture of SCTL batches, we have realized that SCTL inhibits tryptase and trypsin (Fig. 6). This way, we established this inhibitory action of SCTL on the enzymes as a quality control assay for the biochemical standardization of GMP-manufactured SCTL batches [Birr, 2005] .

General Preclinical Considerations on SCTL applications

HTX as a partially hydrolyzed extract of calf thymus containing a mixture of short tissue-specific peptides and SCTL as its synthetic correlate might be compared to thymus peptides regarding their pharmacodynamics.

A number of crude thymus extracts and subsequently purified peptides with distinct biological properties have been prepared from thymus tissue and blood. The most important preparations are summarized in Table 1 [Schulof, 1985, Cazzola et al., 1987].

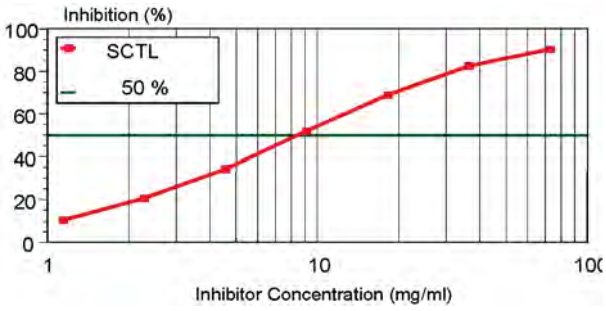


Fig. 4. **Inhibitory Activity of SCTL on Tryptase**

Action of Thymic Factors on T-cells

All of the naturally occurring thymus peptides mentioned above have been shown to augment T cell number and to modulate various T cell functions in man. Although many of the known thymic factors have similar activities in certain biological assays, it is likely that the respective thymic factors act essentially at different steps of the T-cell maturation [Cunningham-Rundles et al., 1999]. In general, studies utilizing peripheral blood lymphocytes were aimed at assessing the influence of thymic factors on either T cell number or on T cell function, as well as on the maturation and differentiation of pre-T lymphocytes [Birr, 1993, 1994, 1996; Ciardelli et al., 1982].

Table 4. **Thymic Factors isolated from thymus tissue and characterized**

Name	Abbr.	Content, size	Status	Origin
Thymosin		Mixture of polypeptides	Crude	Rat thymus
Thymic factor X	TFX	Mixture of polypeptides, MW rang-ing: 2,000-18,000 D	Crude	Calf thymus
Thymosin fraction 5	TF5	10 Major and 30 minor polypeptides	Purified	Calf thymus
Thymostimulin	TP-1	Mixture of polypeptides, MW rang-ing: 1,000-12,000 D	Purified	Calf thymus
Thymomodulin		Mixture of peptides	Purified	Calf thymus
Prothymosin-α α,	Ta	113 amino acids	Purified	Rat thymus
Thymopoietin	TP	Polypeptide, 5,562 D	Purified	
Thymulin, Facteur Thymique Serique	FTS- Zn	Nonapeptide, 847 D	Purified	Pig serum

Abbr.: abbreviations; D: Daltons.

Effects of SCTL on Peripheral Blood Lymphocytes

The T cell activating property of SCTL was compared to that of HTX in two independent studies after prestimulation by phythemagglutinin (PHA; 0.05–0.4 μg/ml).

In one study performed with blood from only 2 donors, SCTL (25–100 μg/ml) increased the proliferation rate (e.g. by approx. 110% at 100 μg/ml), whereas HTX (25–100 μg/ml) caused a dose-dependent inhibition (e.g. by approx. 53% at 100 μg/ml) [Hirt, ORPEGEN 1996; Ho et al., 1987].

Substance	Dose (μg/ml)	Effect	Significance
Control	0	1	$P \leq 0.01$
PHA	0.4	2.33	
SCTL	10	1.38	$P = 0.03$
SCTL	50	1.46	
SCTL	100	1.82	
SCTL	200	1.49	
SCTL	500	1.21	

In the other study with blood of four donors, SCTL did not affect lymphocyte proliferation up to a dose of 500 μg/ml [Maurer, 1999]. HTX (10–500 μg/ml) exhibited the tendency to inhibit cell proliferation in a dose-dependent manner, but this effect was not statistically significant at the 5% level even at the highest concentration. When the effects of HTX and SCTL on lymphocyte proliferation were investigated in the absence of PHA, SCTL significantly stimulated cell proliferation at a single concentration, namely at 100 pg/ml ($P = 0.03$), whereas HTX had no effect. Summarizing these preliminary data, it may be suggested that SCTL and HTX differentially affect lymphocyte proliferation: Some concentrations of SCTL may cause an increase of basal proliferation which is not affected by HTX, whereas stimulated proliferation is virtually not changed by SCTL, but may be inhibited by HTX. However, considering the limited number of individual donors included in these studies a final conclusion cannot be drawn from the present data.

Thymic factors increase the synthesis of soluble mediators by T-cells, most notably, T-cell growth factor (TCGF or IL-2) and gamma Interferon (INF-γ). This cytokine reactivity pattern is defined as T-helper type 1 response. IL-2 is released by activated T- cells and plays a pivotal role in sustaining both proliferative and cytotoxic immune responses. INF-γ augments T-cell cytotoxic activity but exhibits antiproliferative effects.

The effect of SCTL and HTX on PHA-induced and basal IL-2 secretion was investigated in human blood samples [Maurer, 1999].

In the presence of PHA (2.0 μg/ml), HTX (10–500 μg/ml) was ineffective. Only at the highest concentration used, SCTL (10–500 μg/ml) diminished IL-2 secretion, though without statistical significance ($P = 0.09$). In the absence of PHA, no statistically significant effects could be observed with either compound. However, the present data may suggest that by increasing the number of determinations/group (only 3 blood samples/group were used in the present study) a stimulation of IL-2 secretion by each compound might become statistically significant.

In another series of experiments, the effect of SCTL and HTX on IL-2-induced cytotoxicity was compared with each other [Maurer, 1999]. Leukocyte YT-cells with properties similar to natural killer (NK) cells were used in this study. YT-cells were co-incubated with K 562 target cells (20:1) preloaded with calcein AM fluorescence dye. Calcein release was used as a measure of cytotoxicity. SCTL (10, 50, and 250 μg/ml) decreased the cytotoxicity induced by IL-2 at each concentration investigated ($P < 0.01$), whereas HTX (10, 50, and 250 μg/ml) reduced cytotoxicity only at the highest concentration used ($P < 0.05$). In summary, both SCTL and HTX may inhibit IL-2 mediated cytotoxicity, the latter, however, with much lower potency.

In conclusion, thymic factors, HTX and SCTL increase the number of peripheral blood lymphocytes, activate mature and precursor cells and increase the production of IL-2 and

INF-γ via T-helper type 1 response mechanism. Possibly, thymic factors, HTX and SCTL may be capable of exerting a homeostatic role in diseases associated with an imbalance of immunoregulatory T-cell activity. It seems that, for example, well defined thymic peptides like Thymosin-α_1 [Birr et al., 1979] may be required for an early step of cortical thymocyte maturation, whereas the other defined peptide, TP-5 appears to be involved in later stages.

Local Tolerance

Examining SCTL for acute skin irritation in rabbits the fur was removed by shaving from the dorsal area of the trunk of the animals approximately 24 h before the test. Care was taken to avoid abrading the skin; only animals with intact skin were used.

A dose of 500 mg was applied on the test side and then covered with a gauze patch, which was fixed with non-irritating tape for 4 h. The surrounding untreated skin served as a control. The skin sites were evaluated before the application of the test substance. After the exposure period the patch was removed and the skin was evaluated. Scores were taken 60 min as well as 14, 48 and 72 hours after removal. Under the present conditions none of the 3 rabbits exposed to 500mg SCTL showed substance related lesions. There were also no systemic intolerance reactions observed [Leuschner, 1997].

Moreover, SCTL and HTX were also tested in the EpiDerm®Skin Model (MatTek Corporation, Ashland, USA) for dermal irritation. This model consists of several layers of human keratinocytes and mimics human skin. The model substitutes for animal models used for testing skin irritation. In this model HTX and SCTL in a concentration of 10% in aqueous solution were not skin irritating [NeuroBiotec, 2005].

Toxicity

Acute toxicity of SCTL was investigated after a single i.v. injection to rats [Leuschner, 1997]. A dose of 10mg/kg for the rat was used in the experiment. The appropriate solution was administered once i.v. at the above mentioned dose to 1 group of 10 animals. Subsequently the animals were observed at 5, 15, 30 and 60 minutes as well at 6 and 24 hours after the administration. After a 14 day observation period the animals were autopsied. No animal died, and in none of them any substance related findings were observed. Also at autopsy no findings were noted. The LD 50 could not be calculated yet, because not lethality had occurred in the rats. Repeated dose toxicity studies have not been performed so far for SCTL.

In summary, the study reveals a very low if any acute intravenous toxicity of SCTL. Deducted from this it is very unlikely that topical application of SCTL in lotions or cremes can cause toxicity.

The mutagenic potential of SCTL was examined in Salmonella typhimurium strains TA 98, TA 102, TA1535 and TA 1537, without and with metabolic activation by Aroclor. In the first experiment after treatment with 10000 µg SCTL/plate without metabolic activation complete cytotoxicity was observed for tester strain TA 102.

In the second experiment with metabolic activation complete cytotoxicity was observed for tester strains TA 98, TA 102 and TA 1537. A marginal toxicity was observed at the same dose for TA 1535 in both experiments and for the strains TA 98 and TA 1537 in the first experiment. A marginal cytotoxicity had been observed at 3160 µg/plate for the tester strain TA 1537.

In these experiments no mutagenic effect was observed for SCTL tested up to cytotoxic concentrations (3160 and 10000 µg/plate) in any of the 5 tester strains in two independent experiments with and without metabolic activation [Leuschner, 1997].

Preliminary Considerations on Clinical SCTL Applications

The GMP-based standardized manufacture of the drug substance SCTL has been established. The Common Technical Document on SCTL has been compiled by ORPEGEN and presented at the FDA and the German BfARM for an IND approval on applications in clinical trials of different hair loss etiologies by the sponsor.

The author is aiming at clinical applications of SCTL in repairing the destructions of the cellular immune response resulting from virostatic and cytostatic chemo- and X-ray therapies. To date positive results are available only from private treatment of patients having suffered from opportunistic infections after chemotherapy. SCTL will be studied in topic, oral and parenteral applications probably at the NCT Heidelberg.

In another study towards prevention or reduction of alleric responses, the application of SCTL as a dietary supplement is considered. However, sponsors for these clinical applications of SCTL have not yet been identified.

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General remark: In other publ. GKL-02 stands for SCTL, and GKL-01 for HTX, respectively.

РОЗРОБЛЕННЯ ЛІКАРСЬКОЇ СУБСТАНЦІЇ НА ОСНОВІ ГМФ (SCTL) ДЛЯ ПРОФІЛАКТИКИ ОПОРТУНІСТИЧНИХ ІНФЕКЦІЙ ПІСЛЯ РЕНТГЕНІВСЬКОГО ОПРОМІНЕННЯ ТА ХІМІОТЕРАПІЇ РАКУ. ЗАМІНА БІБЛІОТЕКИ СИНТЕТИЧНОГО КОМБІНАТОРНОГО ТЕТРАПЕПТИДУ НА ЕКСТРАКТ ТИМУСА ТЕЛЯТИ

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SCTL є повністю синтетичним корелятом частково ензиматично гідролізованого екстракту тимуса теляти. Аби повністю виключити передачу бичачого пріонного енцефаліту за введення екстрактів тимуса, було створено продукт, який є повністю синтетичним корелятом активних компонентів гідролізату тканини тимуса, — SCTL. Бібліотека цього синтетичного пептиду повністю замінила компоненти екстракту тканини тимуса теляти в декількох косметичних та фармацевтичних препаратах. Активні компоненти SCTL були винаходом автора, однак застосування лікарської субстанції на його основі в косметичній та фармацевтичній промисловості здійснено іншими. Для SCTL описано лише обмежену кількість фармакологічних і токсикологічних властивостей. Було з'ясовано деякі важливі аспекти біологічної активності SCTL, які могли б до певної міри пояснити механізми його дії та клінічної ефективності.

Ключові слова: синтетичний корелят частково ензиматично гидролізованого екстракту тимуса теляти.

РАЗРАБОТКА ЛЕКАРСТВЕННОЙ СУБСТАНЦИИ НА ОСНОВЕ ГМФ (SCTL) ДЛЯ ПРОФИЛАКТИКИ ОППОРТУНИСТИЧЕСКИХ ИНФЕКЦИЙ ПОСЛЕ РЕНТГЕНОВСКОГО ОБЛУЧЕНИЯ И ХИМИОТЕРАПИИ РАКА. ЗАМЕНА БИБЛИОТЕКИ СИНТЕТИЧЕСКОГО КОМБИНАТОРНОГО ТЕТРАПЕПТИДА НА ЭКСТРАКТ ТИМУСА ТЕЛЕНКА

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SCTL является полностью синтетическим коррелятом частично энзиматически гидролизованного экстракта тимуса теленка. Чтобы полностью исключить передачу бычьего прионного энцефалита при введении экстрактов тимуса, был создан продукт, который является полностью синтетическим коррелятом активных компонентов гидролизата ткани тимуса, — SCTL. Библиотека этого синтетического пептида полностью заменила компоненты экстракта ткани тимуса теленка в нескольких косметических и фармацевтических препаратах. Активные компоненты SCTL были изобретением автора, однако применение лекарственной субстанции на его основе в косметической и фармацевтической промышленности осуществлено другими. Для SCTL описано лишь ограниченное количество фармакологических и токсикологических свойств. Были выяснены некоторые важные аспекты биологической активности SCTL, которые могли бы до некоторой степени объяснить механизмы его действия и клинической эффективности.

Ключевые слова: синтетический коррелят частично энзиматически гидролизованного экстракта тимуса теленка.