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Novel Immune-Modulating Peptide to Counteract DNA Damage and Boost Tissue Repair: Advanced Machine Learning Confirmation Over Transcriptomes From 3,250 Patients

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ABSTRACT

Peptides are endogenous protein building blocks that play a pivotal role in the metabolism activating numerous endogenous repair mechanisms. Some peptides span this role controlling putative processes such as the decrease of activity for oxidative enzymes and the upsurge of activity for antioxidant enzymes. In this work, we subject the activity of SH-Oligopeptide-85 SP peptide (Tectum11©) to deep functional analysis using a novel artificial Intelligence system, training it specifically with 3,250 patient transcriptomes from the worldwide reference database Gene Expression Omnibus© (National Centre for Biotechnology Information, NIH USA) to validate its mechanisms of action in penetrating inner tissue structures to decrease the oxidative stress and reduce both global DNA and telomeric damage through inflammatory pathways. Further evidence supporting the use of the SH-Oligopeptide-85 SP peptide (Tectum11©) in patients suffering acute and/ or chronic skin inflammatory skin diseases such as radiodermitis, pruritic skin lesions, xerosis and ichthyosis is also provided.

Keywords: Bio-active peptide(s); Oxidative stress; Acute and chronic skin; Inflammatory skin diseases, Immune modulation

Transcriptomes from 3,250 Patients.RRJ Biol. 2024; 12:008.

INTRODUCTION

Dermatitis, sometimes referred as eczema, belongs to the group of chronic inflammatory skin diseases characterized by red pruritic skin lesions, xerosis, ichthyosis and skin pain. Although the pathological process leading to dermatitis is not yet fully known, a combination of epidermal barrier dysfunction and immune dysregulation are widely regarded as the underlying motives [1]. In this sense, the list of factors that contribute to the instauration of dermatitis ranges from genetic factors and dietary choices to immune triggers and environmental factors. Consequently, research aimed at developing novel effective treatments may be the only resolution to this burdensome disease, more so since the most widely spread treatments rely on the use of topical corticosteroids to relieve local symptoms (2). A general revision of the most common treatments includes indomethacin and oral non-steroidal anti-inflammatory drugs as well as the aforementioned corticosteroids, which are commonly used for long periods in order to help reduce pain and oedema [2,3].

During the physiological processes leading to chronic inflammatory the skin diseases and pruritic lesions, such as xerosis, ichthyosis, and skin pain, normally referred as dermatitis, localized immune and phagocitic cells escape from the status defined as dermatologic equilibrium in which the damaged tissue and immune system reach a dynamic balance where organized cell growth overcomes elimination of dead tissue [4,5]. The point at which the dermatologic equilibrium is lost largely depends on the interactions between those cells and the Extracellular Matrix (ECM) which embeds the three key elements of immune modulation: The Mesenchymal Support Cells (MSC), the Endothelial Cells (EC) and the infiltrated Inflammatory Immune Cells (IIC).

The development of new “omics” techniques (transcriptomics, proteomics, metabolomics and metagenomics) have started to map out the cross-talks between those elements had to depict the routes leading to the formation of a healthy architecture of the new tissue and overcoming the unhealthy microenvironment characterized by a corrupted ECM and chronic inflammation [6]. In particular, radiodermatitis lesions provide a perfect model for understanding this process since healing is difficult due to the scarcity of granulation tissue and the imbalances in activity for ECM, MSC, EC and IIC that may require surgical debridement and/or grafting of healthy skin. Particularly, the presence of inflammatory lesions, leading to dermatitis has been demonstrated to also cause genetic instability, epigenetic modification and ultimately cease of cell proliferation in the area. Likewise, chemical imbalance of the EMC will affect the previous immune modulation causing the modification of anti-apoptotic pathways, reducing the angiogenesis and ultimately, stopping the skin healing process completely [7].

Curiously enough, transcriptomic and proteomic studies suggest that the use of precision bio-peptides may be a defining element to modulate the immune system's responses to the aforementioned harmful stimuli, placing a viable alternative to corticotherapy. In that sense, the use of precision bio-peptides has also been reported as a powerful method to counteract the numerous side effects of corticotherapy such as skin and hair changes, increase of weight, osteoporosis, blood pressure problems and digestive disturbances. Those effects have been discussed to operate through two different general pathways: A) the modulation of inflammation that is needed to maintain the status-quo formerly referred as dermatologic equilibrium [4,5]. B) the systemic immune-inflammation stimulation of the localized immune responses activated by increases in the concentration of Reactive Oxygen Species (ROS) [6].

In this context, the new “omics” techniques (in particular proteomics and metabolomics) and metagenomics have identified the mechanisms activated by an increased concentration of ROS as the two key switch that regulates the dynamic process underlying the modification of the anti-apoptotic pathways which reduces the angiogenesis, and, ultimately, stops the skin healing process. Furthermore, the upsurge of ROS has been confirmed by the aforementioned techniques to correlate with different epigenetic changes in the telomeres [7,8]. A second trigger point identified by such new techniques aims at the systemic immune-inflammation, a condition caused by the upsurge of ROS manifesting through a localized increase in the amount of inflammatory cells (neutrophils, lymphocytes, monocytes) migrating to the skin area where the pruritic lesions, such as xerosis, ichthyosis, and skin pain occur. This effect can affect both individual cell lines and the combined ratio of Neutrophils Lymphocytes (NLR) leading to a decrease of their functional effects as key mediators of a healthy [9].

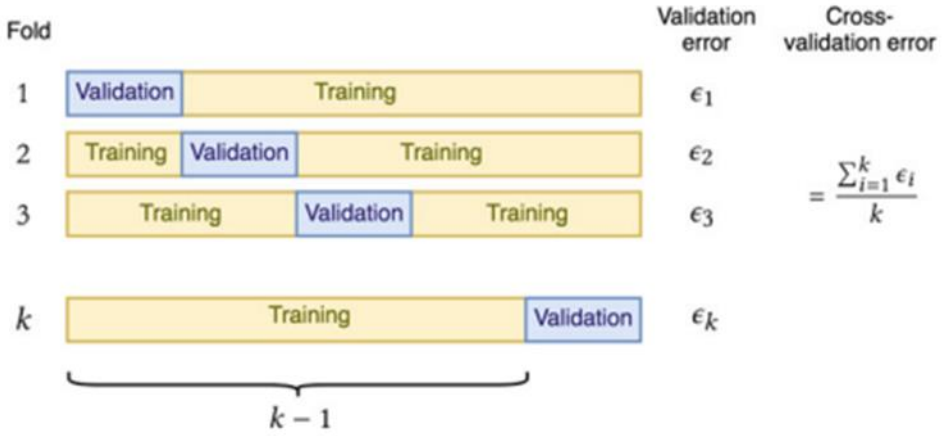
Curiously enough, a former clinical study has identified the SH-Oligopeptide-85 SP peptide (Tectum11©) as a potential precision solution to the aforementioned condition *via* two general pathways: A) the reduction of ROS levels and b) the decrease and/or modulation of systemic inflammation [10]. Taking into account that the effects and suggested mechanisms of action for the SH-Oligopeptide-85 SP peptide (Tectum11©) show clear overlap with the two trigger processes identified by proteomics and metabolomics, we decided to use that information to train a second-generation advanced machine learning engine AI-scythech daresbury to challenge the effects the SH-Oligopeptide-85 SP peptide (Tectum11©) in penetrating inner tissue structures to decrease the oxidative stress and reduce both global DNA and telomeric damage. The AI executed a search over 3,250 chronic inflammatory skin diseases (1,250-RD) for radiodermitis, (1,000-PSL) for pruritic skin lesions and (1,000-XIS) for xerosis, ichthyosis, and skin pain cases within a cancer-patient-model whose a) transcriptomes were modelled from NCBI’s Gene Expression Omnibus© and b) proteomes were modelled from uniprot’s proteome Database©. A deep AI-driven correlation analysis was specifically aimed to explore whether the SH-Oligopeptide-85 SP peptide (Tectum11©) synergised with the reduction of ROS levels ROS and immune modulation acknowledged to account for progression to healing in chronic inflammatory skin diseases.

MATERIALS AND METHODS

The second-generation system for advanced machine learning engine AI-scythech daresbury was trained to look for correlations between the effects of SH-Oligopeptide-85 SP peptide (Tectum11©) over 3,250 chronic inflammatory skin diseases (1,250-RD) for radiodermitis, (1,000-PSL) for pruritic skin lesions and (1,000-XIS) for xerosis, ichthyosis, and skin pain cases within a cancer-patient-model of transcriptomes from NCBI’s Gene Expression Omnibus©. The Teaching and Training (T&T) method used for model validation followed the k-fold cross validation (k-fold CV) standard, in order to reduce the over-fitting of the optimisation of the algorithm used in the grouped analysis (i.e. (1,250-RD) GROUP 1, (1,000-PSL) GROUP 2 and (1,000-XIS) GROUP 3). To achieve this, a 3-fold CV was implemented for T&T splitting the whole dataset into 3 folds and training the Artificial Intelligence (AI) a total of 3

times or T&T rounds. In each T&T round, we iteratively left one different fold out for validation, training the IA over the remaining 2 folds applied according to the three groups of modelled chronic inflammatory skin diseases (I.e. (1,250-RD) GROUP 1, (1,000-PSL) GROUP 2 and (1,000-XIS) GROUP 3). Although in normal practice a k=5 or 10 is used. The extreme amount of data for 3,250 modelled cases forced a 3-fold CV (Figure 1).

Figure 1. k=3-fold cross-validation as described by Weng (CSAIL, MIT, Cambridge, MA, USA) in using data science for global health L. A.



After the AI training, an evaluation of correlation between the effects SH-Oligopeptide-85 SP peptide (Tectum11©) over 3,250 chronic inflammatory skin diseases ((1,250-RD) GROUP 1, (1,000-PSL) GROUP 2 and (1,000-XIS) GROUP 3) within a cancer-patient-model of proteomes modelled from uniprot's proteome Database© was performed, finding that the trained engine was able to correctly discern within the unseen testing data and confirming both the low bias and low variance of the trained AI and the model for analysis (Table 2).

A free tutorial for readers to acquire hands-on visibility on the entire process of T&T, the resulting algorithm used by the AI-scythech daresbury over the patient-based model and the toolkits for clinical validation of the resulting claims is available through the Breast Cancer Wisconsin (Diagnostic) Database. A Cross Entropy/Log Loss function was used for T&T of the AI as depicted in Table 1.

Table 1. Examples of commonly-used loss functions in machine learning as described by Weng [CSAIL, MIT, Cambridge, MA, USA] in Leveraging Data Science for Global Health.

Task	Error type	Loss function	Note
Regression	Mean-squared error	$\frac{1}{n}\sum_{i=1}^{n}(y_i - y_i^2)^2$	Easy to learn but sensitive to outliers (MSE, L2 loss)
	Mean absolute error	$\frac{1}{n}\sum_{i=1}^{n} \mid y_i - y_i^2 \mid$	Robust to outliers but nut differentiable (MAE, L1 loss)
Classification	Cross entropy =log loss	$-\frac{1}{n}\sum_{i=1}^{n}\left[y_i \log(y_i^2) + (1-y_i)\log(1-y_i^2)\right] = -\frac{1}{n}\sum_{i=1}^{n} p_i \log q_i$	Quantify the difference between two probability
	Hinge loss	$\frac{1}{n}\sum_{i=1}^{n}\max(0.1 - y_i y_i^2)$	For support vector machine
	KL divergence	$D_{KL}(p \parallel q) = \sum_i p_i(\log \frac{p_1}{q_1})$	Quantify the difference between two probability distributions

Table 2. Reference data for the RSBD database used for cross-checking of input data of transcriptomes modelled from NCBI's Gene Expression Omnibus© corresponding to 3,250 chronic inflammatory skin diseases ((1,250-RD) for radiodermitis, (1,000-PSL) for pruritic skin lesions and (1,000-XIS) for xerosis, ichthyosis, and skin pain) cases within a patient-model using the AI engine developed by AI-Scythech Daresbury that had been formerly used for the training and validation following the 3-fold CV.

RSBD database	Description of basic parameters
Measurement(s)	Relationships between chemicals and genes • Relationships between diseases and genes • Relationships between diseases and phenotypes • Relationships between genes and phenotypes
Technology type(s)	The Comparative Toxicogenomics Database (CTD) and DrugBank • DisGeNET, UniProt, The Comparative Toxicogenomics Database (CTD), Orphanet, ClinGen, Genomics England, NCBI ClinVar, The Human Phenotype Ontology (HPO), the GWAS Catalog, GWASdb28, the LHGDN and BeFree system • The Human Phenotype Ontology (HPO) and Genetic and Rare Diseases Information Center (GARD)
Sample characteristic organism	*Homo sapiens*

In order to make calculations as accurate as technically possible the RSBD database containing curated, inferred, literature-based information on curated disease genes, phenotypes, and phenotype genes as the direct molecular signatures of rare skin diseases was used. Currently, the Rare Skin Disease Database (RSDB) contains over 900 rare skin diseases, 28,077 genes, 9,732 phenotypes and 17,297 compounds with 16,411 disease-gene relationships, 15,793 disease-phenotype relationships, 12,184 disease-reference relationships, 641,789 gene-phenotype relationships, 17,636 gene-reference relationships and 61,282 references. The RSDB is updated twice a year in June and December and can be visited *via* the RSDB homepage to explore the data for skin disease information.

The aforementioned T&T design was implemented over the RSDB instead of a traditional ad-hoc healthcare data analytics to avoid rare metrics and save the expert-intensive efforts required to design hand-crafted features for collecting data from patients. In summary, the AI engine was successfully trained over the 3,250 transcriptomes modelled from NCBI's Gene Expression Omnibus© By the end of the T&T it showed good performance on the unseen testing data for the cases included within the cancer-patient-model of 3,250 proteomes modelled from uniprot's proteome Database©. A standard Cross Entropy/Log Loss function was used to confirm both the low bias and low variance of the T&T and the resulting model for analysis, thus allowing the utilization of the RSBD database to challenge the pathways described for action of SH-Oligopeptide-85 SP peptide (Tectum11©) with the data for skin disease information.

RESULTS

After successfully training the AI engine developed by AI-scythech daresbury that had been formerly used for the training and validation following the 3-fold CV described above, unseen data for the 3.250 patient-modelled proteomes from uniprot's proteome Database© were scrutinised. Expression patterns for chronic inflammatory skin

diseases ((1,250-RD) for radiodermitis, (1,000-PSL) for pruritic skin lesions and (1,000-XIS) for xerosis, ichthyosis, and skin pain) detected at proteomic level were re-confirmed over the 3.250 transcriptomes modelled from NCBI's Gene Expression Omnibus© the AI engine was trained over. Re-analysis against the reference data for the RSBD database used for cross-checking of input data of transcriptomes modelled from NCBI's gene expression Omnibus© confirmed a series of pathways a) some entirely new and some b) some formerly described for action of SH-Oligopeptide-85 SP peptide (Tectum11©). The following conclusions were drawn from the unseen 3,250 patient-modelled data with both a very low bias and low variance in agreement with the same low values obtained during the T&T process of the AI used for analysis: The SH-Oligopeptide-85 SP peptide (Tectum11©) is confirmed to synergise with the protein effectors (targets) listed in Table 3 to achieve a reduction of ROS levels over 3,239 of the 3,250 patients modelled for chronic inflammatory skin diseases ((1,250-RD) for radiodermitis, (1,000-PSL) for pruritic skin lesions and (1,000-XIS) for xerosis, ichthyosis, and skin pain).

The SH-Oligopeptide-85 SP peptide (Tectum11©) is confirmed to synergise with the protein effectors (targets) listed in Table 4 to achieve immune modulation accountable for progression to healing in chronic inflammatory skin diseases over 3,220 of the 3,250 patients modelled for chronic inflammatory skin diseases ((1,250-RD) for radiodermitis, (1,000-PSL) for pruritic skin lesions and (1,000-XIS) for xerosis, ichthyosis, and skin pain) (Figure 2).

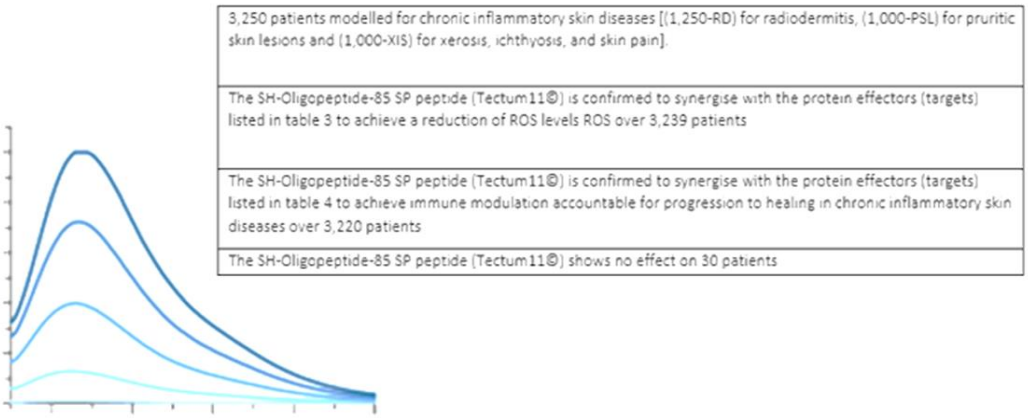
Table 3. Effects in relation to ROS (column-1), targets (column-2) over which the effects are exerted and general actions (column-3) of the targets' activities in response to the SH-Oligopeptide-85 SP peptide (Tectum11©) detected over 3,239 of the 3,250 patients modelled for chronic inflammatory skin diseases [(1,250-RD) for radiodermitis, (1,000-PSL) for pruritic skin lesions and (1,000-XIS) for xerosis, ichthyosis, and skin pain] and confirmed with the reference data for the RSBD database used for cross-checking of input data of transcriptomes modelled from NCBI's Gene Expression Omnibus©.

Effect of SH-Oligopeptide-85 SP peptide (Tectum11©)	Target of peptide Tectum11©'s activity	Action registered for peptide Tectum11© over 3,239 of the 3,250 patients modelled
Induction of target's activity	HIF-2α	ROS homeostasis
Induction of target's activity	PGC-1α	Activation of antioxidative enzymes
Induction of target's activity	Nrf2	Limitation of ROS production
Induction of target's activity	Ucp2	Limitation of inflammation *via* ROS production in macrophage
Reduction of target's activity	TLR1, 2, 4	Decrease ROS generation in macrophage
Reduction of target's activity	NOX2	Decrease mitochondrial ROS production
Reduction of target's activity	MMP-3	Reduction of DNA damage and genomic instability
Reduction of target's activity	EST-1	Decrease ROS generation

Table 4. Effects in relation to immune modulation (column-1), targets (column-2) over which the effects are exerted and general actions (column-3) of the targets' activities in response to the SH-Oligopeptide-85 SP peptide (Tectum11©) detected over 3,220 of the 3,250 patients modelled for chronic inflammatory skin diseases [(1,250-RD) for radiodermitis, (1,000-PSL) for pruritic skin lesions and (1,000-XIS) for xerosis, ichthyosis, and skin pain] and confirmed with the reference data for the RSBD database used for cross-checking of input data of transcriptomes modelled from NCBI's Gene Expression Omnibus©

Effect of SH-Oligopeptide-85 SP peptide (Tectum11©)	Targets of peptide Tectum11©'s activity	Action registered for peptide Tectum11©over 3,239 of the 3,250 patients modelled
Modulation of secretion pattern	IL-4 and IL-13 cytokines	Increase of ECM's soluble: TGF-β, CCL17, CCL22, PDGF-BB
Modulation of secretion pattern	LPS, immune complexes, IL-1Ra and TLR ligands	Increase of ECM's soluble: IL-10, IL-6, IL-1β, CCL1, TNFSF14 TNFα, NOS, MMPs
Modulation of secretion pattern	IL-10 and glucocorticoids	Increase of ECM's soluble: TGF-β, IL-10, MMP-9, IL-1β

Figure 2. Graphical qualitative representation of broad analysis. Dark blue upper curve corresponding to the 3,250 patients modelled for chronic inflammatory skin diseases ((1,250-RD) for radiodermitis, (1,000-PSL) for pruritic skin lesions and (1,000-XIS) for xerosis, ichthyosis, and skin pain).



Lighter blue curve below corresponding to 3,239 of the 3,250 patients positively showing to effects in relation to ROS as per table 3. Lighter blue curve below corresponding to 3,220 of the 3,250 patients positively showing to effects in relation in relation to immune modulation as per Table 4. Lighter blue curve below corresponding to 30 patients showing no effects to SH-Oligopeptide-85 SP peptide (Tectum11©). Breaking down both areas of action and response to SH-Oligopeptide-85 SP peptide (Tectum11©) ((a) effects which are exerted over ROS and general actions of ROS-mediated mechanisms in column-3 of Table 3 and (b) effects which are exerted over immune modulation and general actions of immune-mediated inflammation in column-3 of Table 4, a solid statement about activation *via* both of a variety of Matrix Metalloproteinases (MMPs) can be made. Likewise, a stimulation in secretion of the Vascular Endothelial Growth Factor (VEGF) to the ECM can also be supported; thus causing a recovery of the dynamic balance where skin-healing immunity controls cell growth. Those cascades of positively retro-fed interactions in the ECM directly lead to the activation of the mesenchymal support cells, the endothelial cells, and the infiltrated inflammatory immune cells which are needed for the recovery of tissue architecture and cease of chronic inflammation in skin diseases such as the ones modelled in this analysis ((1,250-RD) for radiodermitis, (1,000-PSL) for pruritic skin lesions and (1,000-XIS) for xerosis, ichthyosis, and skin pain).

Furthermore, data from Table 4 in relation to IL-4 and IL-13 related cytokines coincide with clinical data about immunoreactivity for IL-13- dependent overexpression of TNF-α and IL-3 on endothelial and perivascular cells of the upper dermis in a wide variety

of acute lesions. That regulatory loop opens a wider indication for broader use of the SH-Oligopeptide-85 SP peptide (Tectum11©) in the active modulation of lesioned skin upregulation for acute conditions, where TNF-α and IL-13 play a key role controlling the endothelial and perivascular cell expression of IL-8 as a trigger point for the generation of granulation tissue. Based on the data, the SH-Oligopeptide-85 SP peptide (Tectum11©) is identified as an active promoter for the generation of new connective tissue and microscopic blood vessels that form on the surfaces of a wound during the healing process. Such structure is normally known as granulation tissue and typically grows from the base of an affected skin area and is able to fill wounds of almost any size. These findings suggest that the SH-Oligopeptide-85 SP peptide (Tectum11©) also promotes the segregation of cytokines accountable for consolidation of the granulation tissue, possibly by reducing inflammation in endothelial cells of uninvolved skin and further supporting the use of the SH-Oligopeptide-85 SP peptide (Tectum11©) in patients suffering acute skin diseases and not only chronic lesions.

DISCUSSION

The AI data presented here solidly support the fitness for use the SH-Oligopeptide-85 SP peptide (Tectum11©) in the active modulation of the immune system and reduction of the inflammatory response associated to ROS-related harmful stimuli needed for the cease of acute and chronic inflammation in the group of skin diseases such as the ones modelled in this analysis. Come this point, further clinical evidence and molecular characterisation of the pathways through which the SH-Oligopeptide-85 SP peptide (Tectum11©) synergise with the protein effectors listed in table 3 to achieve a reduction of ROS levels should be pursued. In the same line, further clinical evidence and molecular characterization of the pathways through which the SH-Oligopeptide-85 SP peptide (Tectum11©) is able to achieve immune modulation accountable for progression to healing in acute and chronic inflammatory skin diseases ought to be pursued. In doing this, the predictions based on the data reported here by the second-generation advanced machine learning engine developed by AI-scythech daresbury would gain further clinical support through routine use.

CONCLUSION

In summary, his work highlights the usefulness of AI-driven analysis as a viable substitute of traditional ad-hoc healthcare data analytics, usually involving expert efforts for designing and collecting data. Conclusions drew from the machine learning-based model have solidly validated previous clinical observations and have helped recognize patterns inside the data that advice for treatment with the SH-Oligopeptide-85 SP peptide (Tectum11©) in acute and chronic inflammatory skin diseases such as radiodermitis, pruritic skin lesions, xerosis and ichthyosis. Furthermore, greater understanding of the mechanisms underlying the clinical observations formerly described have been provided in relation to the peptide's capability to synergise with the protein effectors such as the ones listed in table 3 to achieve a reduction of ROS levels. Likewise, deeper understanding of the mechanisms underlying the progression to healing in chronic inflammatory skin diseases *via* immune modulation induced by the peptide have been clearly mapped.

In this context, a solid advice toward uses of the SH-Oligopeptide-85 SP peptide (Tectum11©) in chronic inflammatory skin diseases can be made in order to gain father clinical probation and effectively relieve the pain in patients suffering chronic inflammatory skin diseases such as radiodermitis, pruritic skin lesions, xerosis and ichthyosis.

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