

RESEARCH MONOGRAPH . COMPOUND PROFILE

Vilon

A synthetic dipeptide (L-Lys-L-Glu) derived from structural analysis of the thymic polypeptide complex Thymalin, developed at the Saint Petersburg Institute of Bioregulation and Gerontology as the smallest bioactive peptide bioregulator with immunomodulatory, geroprotective, and epigenetic chromatin-reactivation activity in aging immune cells.

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ABSTRACT

Vilon (L-lysyl-L-glutamic acid; KE dipeptide; CAS 45234-02-4; molecular formula $C_{11}H_{21}N_3O_5$; molecular weight 275.30 g/mol) is a synthetic dipeptide bioregulator developed by Vladimir Khavinson and colleagues at the Saint Petersburg Institute of Bioregulation and Gerontology as the minimal pharmacophore unit of the thymic polypeptide extract Thymalin. The compound represents the shortest bioactive peptide characterized in the Khavinson bioregulatory peptide class, consisting of a single lysine residue bonded to a single glutamic acid residue in the alpha-peptide linkage. Despite its minimal chain length, Vilon has demonstrated reproducible immunomodulatory, anti-tumor, geroprotective, and epigenetic activity across more than two decades of experimental investigation conducted primarily in Russian academic institutions and published in the Bulletin of Experimental Biology and Medicine, Biogerontology, Advances in Gerontology, and the International Journal of Molecular Sciences. The principal molecular mechanism, characterized by Lezhava, Khavinson, and Jokhadze in a series of cytogenetic studies from 2003 to 2023, is sequence-specific binding to the tetranucleotide motif TCGA in gene promoter regions, producing deheterochromatinization (decondensation of constitutive and facultative heterochromatin) in aging lymphocytes and thymocytes, with consequent reactivation of ribosomal genes and release of age-repressed transcriptional programs [1, 2, 3]. The immunomodulatory activity, characterized in thymic cell cultures and in the THP-1 monocyte/macrophage cell line, includes upregulation of CD4 and CD5 T-lymphocyte differentiation markers, enhancement of nucleolar organizer region associated

protein expression, stimulation of interleukin-2 gene expression in blood lymphocytes, and suppression of lipopolysaccharide-induced tumor necrosis factor alpha and interleukin-6 release from terminally differentiated macrophages [4, 5, 6]. The geroprotective profile, established in female CBA mice receiving subcutaneous Vilon from 6 months of age through the lifespan, includes increased mean lifespan by approximately 24 percent, increased physical activity and endurance, decreased body temperature, and reduced incidence of spontaneous neoplasms including lung adenomas and lymphomas [7, 8]. Antitumor activity was independently confirmed in a chemically induced rat urinary bladder carcinogenesis model, where Vilon reduced tumor incidence from 75.5 percent to 56 percent and inhibited preneoplastic changes in the urothelial mucosa [9]. Clinical application in the Russian Federation, where Vilon has been used in investigational and observational settings for postoperative immune reconstitution, chronic infection management, geriatric immune support, and adjunctive diabetes mellitus management, has produced reports of insulin dose reduction (mean 9 units) in 150 patients with type 1 diabetes and favorable tolerability with no consistent adverse events across multiple cohort studies [10, 11, 12]. Pharmacokinetic data from intestinal tract and liver homogenate studies demonstrate that the KE dipeptide resists hydrolysis in small intestinal preparations and is only marginally degraded in large intestinal and hepatic preparations, supporting oral and parenteral bioavailability [13]. The compound is not approved by the United States Food and Drug Administration or by the European Medicines Agency. It is not registered as a pharmaceutical product outside the Russian Federation. Research-grade Vilon is supplied by multiple peptide synthesis vendors at greater than 98 percent purity by high-performance

liquid chromatography. This monograph reviews the chemistry, synthesis, and structural characterization of Vilon; the epigenetic and immunomodulatory mechanisms in molecular detail; the pharmacokinetic data; the preclinical geroprotective and antitumor evidence; the clinical observational evidence; sourcing, reconstitution, and stack-interaction considerations; the adverse-event profile; and a comparative assessment of five thymic and immunomodulatory peptide bioregulators (Thymogen, Thymalin, Thymosin alpha-1, Thymulin, Epithalon) against Vilon on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Not assigned. The compound has not received an INN designation from the World Health Organization.

Research name: Vilon.

One-letter amino acid code: KE (Lys-Glu).

Three-letter amino acid code: L-Lys-L-Glu.

Chemical name: L-lysyl-L-glutamic acid; lysylglutamide; lysylglutamic acid.

Chemical Abstracts Service registry number: 45234-02-4.

PubChem CID: 7010502.

Development context: Vilon was designed as a synthetic dipeptide analog of the immunomodulatory activity of Thymalin, the thymic polypeptide extract that is the parent compound of the Khavinson bioregulatory peptide class. The name "Vilon" is the proprietary research designation assigned by the Saint Petersburg Institute of Bioregulation and Gerontology. In the one-letter amino acid code, the compound is designated KE, and this abbreviation is used interchangeably with "Vilon" in the primary research literature [1, 7].

1.2 Structural class and chemistry

Vilon is a linear dipeptide consisting of L-lysine linked to L-glutamic acid through a standard alpha-peptide bond between the alpha-amino group of lysine and the alpha-carboxyl group of glutamic acid. The compound belongs to the short-chain bioregulatory peptide class, a pharmacological category defined by the Khavinson laboratory to describe peptides of 2 to 4 amino acid residues that demonstrate tissue-specific biological activity at nanomolar to micromolar concentrations through direct interaction with DNA and chromatin rather than through classical receptor-mediated signal transduction [14, 15].

Molecular formula: C₁₁H₂₁N₃O₅.

Molecular weight: 275.30 g/mol.

Exact mass: 275.1481 g/mol (monoisotopic).

Physical properties: White to off-white hygroscopic powder. Freely soluble in water. Soluble in dilute aqueous acid and in physiological saline. Sparingly soluble in organic solvents. The compound is supplied as the free base or as the acetate or trifluoroacetate salt depending on the synthesis and purification method; the free base is the pharmacologically active form. The isoelectric point is approximately 6.5, reflecting the balance between the lysine epsilon-amino group (pKa approximately 10.5), the glutamic acid gamma-carboxyl group (pKa approximately 4.1), and the terminal alpha-amino and alpha-carboxyl groups.

Stereochemistry: Vilon contains two stereocenters (the alpha-carbons of L-lysine and L-glutamic acid) and is supplied as the single L,L-diastereomer. The corresponding D,D and mixed D,L diastereomers have not been characterized for biological activity in the published literature. Investigators should confirm chirality by chiral high-performance liquid chromatography or by optical rotation measurement against a reference standard.

1.3 Synthesis

The synthesis of Vilon proceeds by standard solid-phase or solution-phase peptide synthesis. The compound is a simple dipeptide and its preparation does not require unusual protecting-group strategies or coupling conditions. In solution-phase synthesis, Boc-L-lysine(Cbz)-OH or Fmoc-L-lysine(Boc)-OH is activated with a carbodiimide reagent (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide or 1,3-dicyclohexylcarbodiimide) in the presence of hydroxybenzotriazole and coupled to L-glutamic acid gamma-tert-butyl ester alpha-methyl ester or to L-glutamic acid di-tert-butyl ester. Global deprotection (trifluoroacetic acid for Boc chemistry, piperidine followed by trifluoroacetic acid for Fmoc chemistry) yields the crude dipeptide, which is purified by reversed-phase high-performance liquid chromatography and lyophilized. In solid-phase synthesis (Fmoc chemistry on Wang or Rink amide resin), the glutamic acid residue is loaded first, the lysine is coupled in the second step, and the product is cleaved from the resin with trifluoroacetic acid. Yield is typically greater than 90 percent for the coupling step and greater than 80 percent overall after purification. The product is characterized by reversed-phase HPLC (purity typically greater than 98 percent), mass spectrometry (expected [M+H]⁺ at

276.16), and amino acid analysis. The simplicity of the dipeptide structure makes Vilon one of the most economically synthesized research peptides; gram quantities are readily available from commercial peptide suppliers at moderate cost [15].

2. Abstract

Vilon (L-Lys-L-Glu; KE; CAS 45234-02-4) is a synthetic dipeptide bioregulator of thymic origin, representing the minimal immunomodulatory pharmacophore identified by structural analysis of the polypeptide extract Thymalin at the Saint Petersburg Institute of Bioregulation and Gerontology under the direction of Vladimir Khavinson [1, 7]. The compound is the shortest bioactive peptide in the Khavinson bioregulatory class and one of the shortest peptides to demonstrate reproducible tissue-specific biological activity in mammalian systems.

The principal mechanism of action, distinct from classical receptor-mediated pharmacology, involves sequence-specific interaction with double-stranded DNA at the tetranucleotide motif TCGA within gene promoter regions [2, 14]. This interaction produces deheterochromatinization in senescent immune cells, releasing transcriptional programs repressed by age-associated chromatin condensation. The consequence in cultured lymphocytes from elderly human subjects (ages 75 to 88 years) is reactivation of ribosomal genes, decondensation of constitutive and facultative heterochromatin, and restoration of synthetic processes toward levels characteristic of younger tissue [3, 16].

The immunomodulatory profile includes stimulation of thymocyte proliferation and differentiation toward CD4-positive T-helper cells, upregulation of CD5 lymphocyte differentiation markers, elevation of nucleolar organizer region associated protein expression (indicating increased ribosomal biogenesis), and modulation of interleukin-2 gene expression in blood lymphocytes [4, 5, 6]. In the THP-1 monocyte/macrophage model, Vilon suppresses lipopolysaccharide-induced tumor necrosis factor alpha and interleukin-6 production in terminally differentiated macrophages and reduces monocyte adhesion to activated endothelium, suggesting an anti-inflammatory mechanism operating through induction of tumor necrosis factor tolerance [6].

The geroprotective profile in female CBA mice receiving chronic subcutaneous Vilon from 6 months of age demonstrates increased mean lifespan (approximately 24 percent), increased physical activity and thermal endurance, decreased body temperature, and reduced incidence of spontaneous neoplasms [7, 8]. Antitumor activity has been independently confirmed in chemically induced urinary bladder

carcinogenesis in rats [9]. Clinical observational data from Russian cohorts report immunomodulatory benefit in postoperative recovery, chronic infections, and adjunctive diabetes management, with insulin dose reduction averaging 9 units in type 1 diabetes patients [10, 11, 12].

The compound is not approved by any regulatory authority outside the Russian Federation and is not registered as a pharmaceutical product in the United States, the European Union, or other major regulatory jurisdictions. Research-grade Vilon is commercially available at greater than 98 percent purity from peptide synthesis suppliers. Investigators should obtain certificates of analysis confirming identity, purity, and peptide content on every lot.

3. Discovery and Development History

3.1 Origin

The development of Vilon is inseparable from the broader Khavinson bioregulatory peptide program, initiated in the early 1970s at the Military Medical Academy and subsequently at the Saint Petersburg Institute of Bioregulation and Gerontology. Vladimir Khavinson, building on the earlier Soviet tradition of tissue-specific peptide extract pharmacology (derived from the work of V. G. Morozov and others), developed Thymalin as a polypeptide complex extracted from calf thymus tissue with immunomodulatory activity [10, 17]. Thymalin entered clinical use in the Soviet Union and later the Russian Federation as an immunocorrective agent for conditions associated with immune deficiency, including postoperative immune suppression, chronic infections, and immune dysfunction in the elderly.

3.2 Identification of the minimal pharmacophore

Beginning in the 1990s, the Khavinson laboratory undertook systematic amino acid sequence analysis and activity-guided fractionation of Thymalin to identify the minimal peptide sequences responsible for its immunomodulatory activity. This program identified two dipeptide sequences with reproducible biological activity: Glu-Trp (Thymogen, EW), which became a registered pharmaceutical product in the Russian Federation, and Lys-Glu (Vilon, KE) [1, 7, 14]. The identification of biologically active dipeptides from a complex polypeptide extract was a conceptual advance in the Khavinson program, establishing the principle that peptides as short as two amino acid residues could retain tissue-specific bioregulatory activity when the sequence matched critical recognition elements in the target cell genome.

3.3 Experimental characterization (2000 to 2010)

The first major experimental publications on Vilon appeared in 2000 with the Khavinson and Anisimov report on geroprotective activity in CBA mice, published in the Bulletin of Experimental Biology and Medicine [7, 8]. Concurrent publications established the antitumor activity in chemically induced bladder carcinogenesis [9] and the immunomodulatory effects in spleen organotypic cultures from

aged rats [18, 19]. The Lezhava and Khavinson cytogenetic studies on chromatin re-activation in lymphocytes from elderly subjects began appearing in 2003 and continued through the 2010s, establishing the epigenetic mechanism as the principal molecular basis for the age-related immunoprotective activity [3, 16].

3.4 Molecular mechanism elucidation (2010 to 2021)

The molecular mechanism of Vilon was progressively characterized through biophysical studies of peptide-DNA interaction, molecular modeling of dipeptide binding to double-stranded DNA, and gene expression microarray studies. The Khavinson laboratory demonstrated in 2014 that the KE dipeptide showed selective binding to the TCGA DNA sequence in the promoter region of the APG5L gene and other genes involved in immune signaling, cell proliferation, and metabolic regulation [2, 14]. A systematic review published by Khavinson and Popovich in *Molecules* in 2021 synthesized the physical, chemical, molecular modeling, and molecular biology evidence for the peptide-DNA interaction mechanism across the entire Khavinson bioregulatory peptide class, with Vilon as one of the principal exemplars [15].

3.5 Contemporary status

As of 2026, Vilon remains a research compound without regulatory approval outside the Russian Federation. It has been used clinically in Russia in investigational and observational settings for immunocorrection, geriatric support, and adjunctive diabetes management. The compound is commercially available as a research-grade peptide from multiple international suppliers. The primary research literature comprises approximately 30 to 40 publications, predominantly from the Khavinson laboratory and collaborating institutions (the Javakhishvili Tbilisi State University group of Lezhava and Jokhadze, the N.N. Petrov National Medical Research Center of Oncology group of Anisimov, and the Italian THP-1 research group of Robuffo and colleagues). No large-scale, independent, randomized, placebo-controlled clinical trials conforming to International Council for Harmonisation Good Clinical Practice standards have been published in English-language peer-reviewed journals.

4. Mechanism of Action

4.1 Epigenetic chromatin remodeling

The principal molecular mechanism of Vilon, distinguishing it from receptor-mediated peptide pharmacology, is direct interaction with nuclear DNA and chromatin. The Khavinson laboratory and the Lezhava cytogenetics group demonstrated that short bioregulatory peptides, including Vilon, penetrate cell nuclei and nucleoli and interact with chromatin at multiple levels: the nucleosome, histone proteins, and double-stranded DNA [2, 3, 14, 15].

The specific DNA recognition element for the KE dipeptide is the tetranucleotide sequence TCGA, identified by molecular modeling and confirmed by biophysical binding studies. This sequence is found in the promoter regions of multiple genes involved in immune signaling (interleukin-2), cell proliferation (EPS15, MCM10 homolog), autophagy (APG5L), cytoskeletal dynamics (Cullin 5, FUSED), and metabolic regulation [2, 15]. The binding of the KE dipeptide to the TCGA motif produces local chromatin decondensation (deheterochromatinization), converting constitutive and facultative heterochromatin to transcriptionally accessible euchromatin.

In cultured lymphocytes from elderly human subjects (ages 75 to 88 years), Vilon treatment produces measurable cytogenetic changes: unrolling of total heterochromatin, activation of nucleolar organizer regions (indicative of ribosomal gene reactivation), and decondensation of euchromatic regions that had undergone age-associated facultative heterochromatinization [3, 16]. The magnitude of the chromatin reactivation is substantial: in the Lezhava et al. (2004) Biogerontology study, Vilon-treated lymphocyte cultures from elderly subjects showed heterochromatin indices approaching those observed in lymphocytes from younger control subjects [3].

4.2 Gene expression regulation

DNA microarray studies using 15,247-gene chips demonstrated that the KE peptide regulates the expression of a specific subset of genes in mouse heart and brain tissue, distinct from the gene sets regulated by other Khavinson peptides (Thymogen/EW, Epithalon/AEDG, Livagen/KEDA) [2, 14]. The KE-responsive gene set includes genes involved in immune cell signaling (IL2), cell cycle control

(MCM10 homolog), ubiquitin-proteasome pathway (Cullin 5), autophagy (APG5L), signal transduction (EPS15), inositol phosphate signaling (ITPK1), amino acid transport (SLC7A6), transcriptional regulation (ZNF01, MLLT3), and mitochondrial dynamics (Gdap1) [2, 15]. The expression changes are bidirectional, with some genes upregulated and others downregulated by KE exposure, supporting a regulatory rather than a globally activating or suppressing mechanism.

The interleukin-2 gene is of particular immunological significance. The KE dipeptide was shown to regulate IL2 expression in blood lymphocytes, and since interleukin-2 is the principal autocrine and paracrine growth factor for T-lymphocyte proliferation and differentiation, this provides a direct molecular link between the epigenetic mechanism and the observed immunomodulatory phenotype [14, 15].

4.3 Immunomodulatory mechanisms

The immunomodulatory activity of Vilon operates through several convergent pathways downstream of the epigenetic mechanism:

Thymocyte differentiation. In cultured human and rat thymic cells, Vilon increases the expression of CD5 lymphocyte differentiation markers and promotes differentiation of thymocyte precursors toward the CD4-positive T-helper lineage [4, 5]. The CD5 upregulation is a marker of thymocyte maturation and is consistent with Vilon promoting the normal differentiation program of the thymus rather than producing aberrant or dysregulated lymphocyte activation.

Nucleolar organizer region activation. Vilon elevates the expression of nucleolar organizer region (NOR) associated proteins in both thymic epithelial cells and thymocytes [4]. NOR-associated proteins are markers of ribosomal RNA transcriptional activity; their upregulation indicates increased ribosomal biogenesis and protein synthesis capacity, consistent with the reactivation of aged cells toward a more metabolically active state.

T-helper cell activation. Both Vilon and its structural analog R-1 were found to activate T-helper cells in spleen organotypic cultures from old rats, increasing the proportion of functionally active CD4-positive cells in the culture [18, 19].

Anti-inflammatory activity. In the THP-1 monocyte/macrophage cell line (Robuffo et al. 2022, International Journal of Molecular Sciences), Vilon and four other Khavinson peptides suppressed lipopolysaccharide-induced tumor necrosis factor alpha and interleukin-6 production in terminally differentiated

macrophages, reduced monocyte adhesion to activated endothelial cells, and increased tyrosine phosphorylation of mitogen-activated protein kinases [6]. The anti-inflammatory mechanism was characterized as induction of tumor necrosis factor tolerance, a process by which prior peptide exposure renders macrophages less responsive to subsequent inflammatory stimulation.

4.4 Composite pharmacology

The composite mechanism of Vilon is therefore an epigenetic-to-transcriptional cascade: the KE dipeptide enters the nucleus, binds the TCGA motif in gene promoter regions, decondenses local chromatin, restores transcriptional access to age-repressed immune and proliferative genes, and produces downstream immunomodulatory and anti-inflammatory effects through the cumulative action of the re-activated gene products. This mechanism is fundamentally different from classical receptor pharmacology and from the signal-transduction mechanisms of conventional immunomodulatory agents (interferons, interleukins, colony-stimulating factors). The mechanism has been reproduced across multiple laboratories and cell systems but has not been independently validated outside the Khavinson research network by groups with no institutional affiliation to the Saint Petersburg Institute.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption and stability

Formal human pharmacokinetic studies of Vilon conforming to regulatory standards have not been published. The available pharmacokinetic data derive from in vitro stability studies using tissue homogenates. Khavinson and colleagues demonstrated that the KE dipeptide, along with Epithalon (AEDG) and Livagen (KEDA), is not hydrolyzed in small intestinal preparations and is only marginally hydrolyzed in large intestinal and hepatic preparations from rat tissue [13]. This resistance to intestinal proteolysis is attributed to the short chain length (dipeptide transporters such as PEPT1 absorb dipeptides intact before luminal peptidases can act) and to the absence of recognized cleavage sites for the principal brush-border and pancreatic endopeptidases.

The implication is that oral bioavailability may be achievable for the KE dipeptide, a notable property for a peptide compound and one that distinguishes the short-chain bioregulators from longer peptides and polypeptides that are extensively degraded by luminal proteolysis. However, formal oral bioavailability measurements (AUC ratio of oral to intravenous dosing) have not been published.

5.2 Distribution

Tissue distribution studies have not been formally characterized. The small molecular weight (275.30 g/mol) and the hydrophilic character of the dipeptide predict rapid distribution to well-perfused tissues. The nuclear penetration observed in cell culture studies (demonstrated by cytogenetic evidence of chromatin remodeling in intact cells) indicates that Vilon crosses cell membranes and the nuclear envelope, consistent with either passive diffusion of the small uncharged species or active transport by peptide transporters [3, 16].

5.3 Metabolism

As a dipeptide composed of two proteinogenic amino acids, Vilon is expected to be metabolized by ubiquitous intracellular peptidases to its constituent amino acids (lysine and glutamic acid), which then enter standard amino acid metabolic pathways. The metabolic products are endogenous and non-toxic. The biological half-life is expected to be short (minutes to hours), consistent with the rapid turnover of small peptides in plasma and tissues. The short half-life is consistent with the repeated-dosing protocols used in experimental and clinical studies (daily injections for 5 to 10 days).

5.4 Routes of administration

Three principal routes have been reported in the experimental and clinical literature:

Subcutaneous injection: The route used in the principal animal studies (CBA mouse lifespan studies, spleen organotypic culture studies). Typical experimental doses in mice: 0.1 to 1 microgram per animal per injection, administered subcutaneously in physiological saline [7, 8].

Intramuscular injection: The route used in Russian clinical practice. Reported clinical protocol: 10 mg intramuscularly daily for 5 to 10 days, repeated every 3 to 6 months [10, 11, 12].

In vitro addition: The route used in cell culture studies. Typical in vitro concentrations: 20 ng/mL in organotypic culture medium; 2 to 20 ng/mL in lymphocyte and THP-1 cell culture [3, 6, 18].

Oral administration has been explored on the basis of the intestinal stability data but is not the established route in published clinical or preclinical protocols.

5.5 Special populations

No formal pharmacokinetic studies in special populations (pediatric, geriatric, hepatic impairment, renal impairment) have been published. The geriatric population is paradoxically the principal intended target for geroprotective applications, but pharmacokinetic characterization in elderly subjects is absent from the published record.

6. Preclinical Pharmacology

6.1 Geroprotective activity in mice

The seminal geroprotective study was reported by Khavinson and Anisimov in the Bulletin of Experimental Biology and Medicine (2000) [7, 8]. Female CBA mice received subcutaneous Vilon beginning at 6 months of age and continuing throughout the lifespan. The treatment produced the following outcomes compared to saline-treated controls:

- Mean lifespan increased by approximately 24 percent.
- Maximum lifespan was modestly extended.
- Physical activity and endurance on forced-swimming and treadmill tests were significantly increased.
- Body temperature was decreased, a biomarker of caloric-restriction-like metabolic adaptation associated with extended lifespan in multiple rodent models.
- Incidence of spontaneous neoplasms was significantly reduced, including spontaneous lung adenomas and lymphomas.
- Body weight and food consumption were not significantly altered, indicating that the geroprotective effect was not mediated by caloric restriction.
- Estrous function and free radical processes (measured by chemiluminescence of tissue homogenates) were not significantly altered.
- No unfavorable effects on animal development were observed during chronic administration.

The authors concluded that the safety profile of chronic Vilon administration supported its use for geroprotection and prophylaxis of age-related pathology [7, 8].

6.2 Antitumor activity

Spontaneous tumors in CBA mice. The geroprotective study (Section 6.1) demonstrated that chronic Vilon administration significantly reduced the incidence of spontaneous neoplasms in aging CBA mice. The effect on spontaneous lung adeno-

mas was particularly notable, with Vilon-treated animals showing a lower incidence of this common age-associated neoplasm [7, 8].

Chemically induced bladder tumors in rats. Pliss, Mel'nikov, Khavinson, and Anisimov (2001) reported in the Bulletin of Experimental Biology and Medicine that Vilon significantly inhibited the development of chemically induced urinary bladder tumors in rats [9]. In the N-butyl-N-(4-hydroxybutyl)nitrosamine model of bladder carcinogenesis, Vilon treatment reduced tumor incidence from 75.5 percent in control animals to 56 percent in treated animals and produced a two-fold decrease in the incidence of preneoplastic and early neoplastic changes in the urothelial mucosa. The antitumor mechanism was attributed to the immunomodulatory enhancement of tumor immunosurveillance rather than to direct cytotoxicity, consistent with the epigenetic reactivation of immune cell function [9].

6.3 Spleen organotypic culture studies

Korenevsky, Khavinson, and colleagues (2002, 2003) studied the effects of Vilon on organotypic cultures of rat spleen tissue from animals of different ages (3 days, 3 weeks, and 2 years) [18, 19]. Vilon at 20 ng/mL in culture medium produced the following effects:

- Morphological stabilization of the tissue explant, with preservation of architectural integrity during extended culture.
- Activation of regeneration and functional activity of immune cells.
- Stimulation of the stromal microenvironment.
- Significantly increased cell viability in surviving cultures.
- Under stress conditions causing partial cell loss, Vilon decreased cell loss, increased proliferative potential, and enhanced cell resistance to adverse microenvironmental conditions.
- The effects were more pronounced in explants from old animals than from young animals, consistent with the deheterochromatinization mechanism preferentially affecting cells with age-accumulated chromatin condensation.
- Reciprocal regulation of proliferative activity was observed between central and peripheral zones of the spleen organotypic culture, with Vilon modulating the spatial pattern of proliferation in an age-dependent manner.

6.4 Chromatin reactivation in human lymphocytes

The Lezhava, Jokhadze, and Khavinson cytogenetic studies (2003 to 2023) constitute the most detailed characterization of the Vilon mechanism at the cellular level [3, 16]. Lymphocytes were obtained from peripheral blood of elderly human subjects (ages 75 to 88 years) and cultured with or without Vilon. The principal findings were:

- Vilon induced significant decondensation of total heterochromatin in cultured lymphocytes from elderly subjects.
- Ribosomal genes (located in nucleolar organizer regions on the short arms of acrocentric chromosomes) were reactivated, as measured by silver staining of NOR-associated proteins.
- Facultative heterochromatin (euchromatic regions that had undergone age-associated condensation) was decondensed, with release of previously silenced genes.
- The magnitude of chromatin reactivation was dose-dependent and time-dependent over the 48 to 72 hour culture period.
- The cytogenetic changes were specific to the KE dipeptide and were not reproduced by equimolar concentrations of the constituent free amino acids (lysine alone, glutamic acid alone, or the equimolar mixture), establishing that the peptide bond and the specific dipeptide sequence are required for biological activity [3, 16].

7. Clinical Evidence Base

7.1 Immunocorrection in postoperative and chronic infection settings

Vilon has been used in Russian clinical practice for postoperative immune reconstitution and for chronic infections associated with immune deficiency. Published clinical reports describe administration of Vilon at 10 mg intramuscularly daily for 5 to 10 days in patients with postoperative immune suppression, chronic recurrent infections, and geriatric immune dysfunction [10, 11, 12]. The reported outcomes include improvement in T-lymphocyte counts, normalization of CD4/CD8 ratios, and clinical improvement in infection resolution. These reports are predominantly from Russian-language medical literature, are observational or open-label in design, and have not been replicated in independent, randomized, placebo-controlled trials conforming to international standards.

7.2 Diabetes mellitus

Khavinson and colleagues reported the use of Vilon in 150 patients with type 1 diabetes mellitus, including 30 patients older than 50 years [11, 12]. In the treated cohort, a significant proportion of patients were able to decrease their insulin dose by an average of 9 units. The mechanism was attributed to immunomodulatory normalization of the autoimmune process underlying type 1 diabetes rather than to a direct insulintropic or hypoglycemic effect. The study design was observational, without placebo control, and the results have not been independently replicated.

7.3 Geriatric longevity cohort

The Khavinson and Morozov (2003) Neuroendocrinology Letters study reported results of a 6-year clinical observation of elderly patients (aged 60 to 80 years) treated with combinations of Thymalin and Epithalamin (the polypeptide precursors of Vilon and Epithalon, respectively) [17]. Mortality in the treated groups was decreased 2.0 to 2.1 fold compared to untreated controls for Thymalin alone and 1.6 to 1.8 fold for Epithalamin alone; the combination produced a 2.5-fold decrease in mortality. While this study used the polypeptide extract Thymalin rather than the

synthetic dipeptide Vilon, the immunomodulatory activity of Thymalin is attributed in part to the KE (Vilon) and EW (Thymogen) dipeptide sequences it contains, and the clinical results are therefore partially relevant to the Vilon evidence base [10, 17].

7.4 Limitations of the clinical evidence

The clinical evidence for Vilon is characterized by several important limitations:

- No large-scale, randomized, double-blind, placebo-controlled trials have been published in international peer-reviewed journals.
- Published clinical data originate predominantly from a single research network (the Khavinson laboratory and affiliated institutions).
- Most clinical reports are observational, open-label, or retrospective in design.
- Outcome measures are heterogeneous and do not conform to validated clinical endpoint standards used in international regulatory submissions.
- The distinction between the clinical effects of the polypeptide extract Thymalin and the synthetic dipeptide Vilon is not always clearly maintained in the clinical literature.
- Independent replication by groups outside the Khavinson research network has not been published.

Investigators should interpret the clinical evidence in this context and should not extrapolate the observational Russian-language data to clinical efficacy claims in the regulatory sense.

8. Sourcing and Quality Verification

Research-grade Vilon (L-Lys-L-Glu; KE dipeptide) is supplied by multiple peptide synthesis vendors including Peptide Sciences, Biosynth, GenScript, China Peptides, and specialized bioregulatory peptide suppliers. The compound is typically supplied as a lyophilized powder (free base or acetate/trifluoroacetate salt) at stated purity of greater than 98 percent by reversed-phase high-performance liquid chromatography. Quantities range from milligrams to grams; pricing is moderate, in the range of \$30 to \$150 per 20 mg vial at the time of monograph preparation.

Investigators should confirm compound identity and purity on every research-grade lot through:

- Reversed-phase high-performance liquid chromatography area-percent purity, ideally greater than 98 percent.
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ at m/z 276.16 for the protonated free base).
- Amino acid analysis confirming the Lys:Glu ratio of 1:1.
- Chiral HPLC or optical rotation confirming L,L-stereochemistry.
- Peptide content determination (accounting for counterion, water, and salt content; net peptide content is typically 70 to 85 percent of gross weight for trifluoroacetate salts).
- Endotoxin testing (limulus amebocyte lysate assay) for material intended for in vivo or cell culture applications.
- Residual solvent analysis for acetonitrile, trifluoroacetic acid, and other common HPLC and synthesis solvents.

Third-party analytical confirmation is recommended for any investigation where dose-response precision is important. The Vilon research-grade market is less well established than the market for more widely studied peptides, and lot-to-lot variability in peptide content, counterion composition, and residual solvent is expected.

9. Reconstitution and Handling

Vilon is supplied as a lyophilized powder and is reconstituted in sterile water for injection, bacteriostatic water (0.9 percent benzyl alcohol), or physiological saline (0.9 percent sodium chloride). The compound is freely soluble in water at room temperature; reconstitution at concentrations of 1 to 10 mg/mL proceeds without difficulty.

Stock solution preparation: For in vitro cell culture applications, stock solutions are typically prepared at 1 mg/mL (3.6 millimolar) in sterile phosphate-buffered saline or in sterile water for injection. Aliquots of 50 to 100 microliters are stored at minus 20 degrees Celsius. For in vivo applications, working solutions at the intended injection concentration are prepared fresh or from frozen aliquots.

Storage: Lyophilized powder should be stored at minus 20 degrees Celsius or at 2 to 8 degrees Celsius. Reconstituted solutions in bacteriostatic water should be stored at 2 to 8 degrees Celsius and used within 14 to 30 days. Reconstituted solutions in sterile water for injection should be used within 24 to 48 hours and stored at 2 to 8 degrees Celsius. Light protection is not required but is reasonable practice.

Freeze-thaw stability: As a small, stable dipeptide, Vilon is expected to tolerate multiple freeze-thaw cycles without significant degradation. However, aliquoting for single-use is recommended to minimize contamination risk and to avoid potential aggregation of counterion salts.

Compatibility: Vilon is compatible with standard glass and polypropylene laboratory plastics. Adsorption to container surfaces is expected to be minimal given the hydrophilic character and the small size of the molecule. Low-binding polypropylene tubes are recommended for dilute solutions (below 10 micrograms per milliliter) to minimize adsorption losses.

10. Stack Interaction Considerations

Vilon operates through an epigenetic mechanism (chromatin remodeling and gene expression regulation) rather than through receptor-mediated signal transduction. The interaction profile is therefore qualitatively different from that of receptor-targeting drugs and peptides. The following considerations apply to investigators conducting research with Vilon in combination with other compounds:

Other Khavinson bio regulatory peptides: Vilon is frequently studied alongside other Khavinson peptides, particularly Epithalon (AEDG, pineal bioregulator), Thymogen (EW, thymic bioregulator), Livagen (KEDA, hepatic bioregulator), and Cortagen (AEDP, cortical bioregulator). Each peptide binds a distinct DNA sequence motif and regulates a distinct gene set; the combination is expected to produce additive or synergistic effects on the composite gene expression profile. The Robuffo et al. (2022) THP-1 study evaluated multiple Khavinson peptides simultaneously and found comparable anti-inflammatory activity for each, supporting the concept of a cooperative peptide bioregulatory network [6].

Thymic peptides and immunomodulators: Concurrent use of Vilon with Thymosin alpha-1, Thymulin, or recombinant interleukins produces additive immunostimulation. Investigators should monitor for excessive immune activation in models where autoimmune pathology is a concern.

Immunosuppressants: The immunomodulatory activity of Vilon (T-cell activation, cytokine regulation) may antagonize the effects of immunosuppressive drugs (cyclosporine, tacrolimus, mycophenolate, corticosteroids). The interaction has not been formally studied but is predictable from mechanism.

Cytotoxic chemotherapy and radiation: The Khavinson clinical literature describes use of thymic peptide bioregulators (Thymalin, and by extension Vilon) for immune reconstitution following chemotherapy and radiation therapy. The timing of administration relative to cytotoxic treatment is important: concurrent use during active cytotoxic therapy may impair the intended immunosuppressive effect, while post-treatment use for immune reconstitution is the intended application [10, 17].

Melatonin and pineal peptides: A combination of thymic and pineal peptide bioregulators (Thymalin plus Epithalamin) has been studied for synergistic geroprotective effects, including reports of thymic regrowth in a single-subject observation [17, 20]. The combination is mechanistically plausible (thymic reactivation plus pineal melatonin-telomerase effects) and is used in longevity research protocols.

Metabolic agents: No characterized pharmacokinetic interactions are expected with metabolic agents (metformin, rapamycin, NAD⁺ precursors, senolytics) given the absence of cytochrome P450 involvement in Vilon metabolism. Mechanistic interactions (e.g., additive geroprotective effects through complementary pathways) are plausible but uncharacterized.

11. Adverse Events and Safety

11.1 Preclinical safety

The preclinical safety profile of Vilon is notable for the near-complete absence of adverse findings in published animal studies. In the chronic CBA mouse lifespan study (Khavinson and Anisimov 2000), subcutaneous Vilon administered from 6 months of age through the lifespan produced no unfavorable effects on animal development, body weight, food consumption, estrous function, or free radical processes [7, 8]. The compound did not increase the incidence of any neoplasm type and in fact significantly reduced the incidence of spontaneous tumors. No organ toxicity, behavioral toxicity, or reproductive toxicity has been reported in published preclinical studies.

11.2 Clinical safety

No systematic adverse events have been consistently reported in the published clinical literature on Vilon. The compound, as a dipeptide composed of two endogenous amino acids, is expected to have minimal inherent toxicity. Reported clinical use at 10 mg intramuscularly daily for 5 to 10 days has been described as well tolerated, with no serious adverse events documented across published observational cohorts [10, 11, 12].

The following theoretical adverse-event considerations apply:

- **Injection-site reactions:** Mild local reactions (pain, redness, swelling) at the intramuscular injection site are possible but have not been prominently reported.
- **Immune overactivation:** Given the immunostimulatory mechanism, excessive immune activation is a theoretical concern in patients with active autoimmune disease or in the context of concurrent immunostimulatory therapy. This concern has not been clinically validated but is mechanistically plausible.
- **Allergic reactions:** Hypersensitivity to the peptide or to excipients in the formulation is theoretically possible but has not been reported.

- **Counterion toxicity:** Research-grade Vilon supplied as the trifluoroacetate salt contains trifluoroacetic acid as a counterion; chronic administration of trifluoroacetate salts may produce cumulative fluorinated compound exposure. Investigators should consider acetate-salt or free-base formulations for chronic in vivo studies.

11.3 Limitations of the safety data

The safety data for Vilon are limited by the same methodological constraints that affect the efficacy data: small sample sizes, observational study designs, absence of systematic adverse-event collection using standardized instruments (such as the Common Terminology Criteria for Adverse Events), and predominant origin from a single research network. The apparent safety of the compound should be interpreted with appropriate caution given these limitations.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five thymic and immunomodulatory peptide bioregulators against Vilon, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal peptide immunomodulators with substantive pre-clinical or clinical pharmacology programs and with mechanistic relevance to Vilon's thymic bioregulatory function.

12.1 Thymogen (Glu-Trp; EW)

Mechanism: Synthetic dipeptide bioregulator of thymic origin, the Glu-Trp sequence identified alongside Vilon (Lys-Glu) from Thymalin structural analysis. Thymogen operates through a similar epigenetic chromatin-remodeling mechanism but binds a distinct DNA sequence motif and regulates a partially overlapping but distinct gene set. The immunomodulatory activity includes T-lymphocyte differentiation, natural killer cell activation, and interferon production enhancement [10, 14].

Development trajectory: Thymogen is a registered pharmaceutical product in the Russian Federation, approved for immunocorrection in conditions associated with immune deficiency. It has been marketed as an intranasal spray and as an injectable formulation. The registration represents a more advanced regulatory status than Vilon, which has not achieved pharmaceutical registration even in the Russian Federation.

Novelty: Low. The mechanism is essentially identical in concept to Vilon (dipeptide-DNA interaction, chromatin remodeling) but with a different sequence and different target genes.

Effect size: Comparable to Vilon in preclinical immunomodulatory models. Clinical evidence from Russian observational studies shows similar immunocorrective endpoints.

Promising potential: Moderate. Registered in the Russian Federation; not registered internationally. Limited international recognition.

Side-effect profile: Comparable to Vilon: no systematic adverse events reported. The registered pharmaceutical status implies regulatory safety review in the Russian Federation.

Overall validation: Moderate. Pharmaceutical registration in one jurisdiction; absent independent international validation.

Comparison to Vilon: Thymogen and Vilon are sister compounds, both derived from Thymalin, both dipeptides, and both operating through epigenetic mechanisms. Thymogen has the advantage of pharmaceutical registration and intranasal formulation. Vilon has the advantage of the specific geroprotective and antitumor preclinical data (CBA mouse lifespan extension, bladder tumor inhibition) that have not been published for Thymogen.

12.2 Thymalin (thymic polypeptide complex)

Mechanism: Polypeptide complex extracted from calf thymus tissue, containing multiple peptide sequences including the KE (Vilon) and EW (Thymogen) dipeptide motifs. The mechanism is a composite of the activities of the constituent peptides, producing broad immunomodulatory effects including T-cell differentiation, natural killer cell activation, cytokine regulation, and immune reconstitution [10, 17].

Development trajectory: Thymalin is a registered pharmaceutical product in the Russian Federation and has been in clinical use since the 1970s for immunocorrection. It is the parent compound from which Vilon and Thymogen were derived. Clinical cohort data from a 6-year observation of elderly patients showed 2.0 to 2.1 fold reduction in mortality in Thymalin-treated groups versus controls [17].

Novelty: Low. The compound is a tissue extract with a long clinical history.

Effect size: Substantial in Russian observational cohort data (mortality reduction). The composite effect of the polypeptide complex may be greater than that of any single constituent dipeptide.

Promising potential: Low to moderate. Established in Russian clinical practice but unlikely to achieve international registration owing to the complexity and batch variability inherent in tissue-extract pharmaceuticals.

Side-effect profile: Favorable. Decades of clinical use with no consistent safety concerns reported.

Overall validation: Moderate. Long clinical history and pharmaceutical registration in one jurisdiction, but absent international regulatory validation and absent randomized controlled trial evidence conforming to international standards.

Comparison to Vilon: Thymalin is the parent compound from which Vilon was derived. It contains Vilon as one of multiple active components. Vilon has the advantage of being a defined chemical entity with reproducible synthesis and characterization, whereas Thymalin is a complex extract with inherent batch variability. Thymalin has the advantage of a longer clinical history and broader clinical evidence base.

12.3 Thymosin alpha-1 (Thymalfasin)

Mechanism: A 28-amino-acid peptide originally isolated from thymic fraction 5 by Allan Goldstein at George Washington University. Thymosin alpha-1 is an immunomodulatory peptide that acts through Toll-like receptor 9 and Toll-like receptor 2 signaling in dendritic cells and through direct effects on T-lymphocyte maturation and function. The mechanism includes activation of plasmacytoid dendritic cells, enhancement of antibody responses, and promotion of T-cell differentiation [21, 22].

Development trajectory: Thymosin alpha-1 (marketed as Zadaxin by SciClone Pharmaceuticals) has been approved in more than 35 countries for the treatment of hepatitis B and as an immunomodulatory adjunct. It has the most extensive international regulatory history of any thymic peptide. Clinical trials in hepatitis B, hepatitis C, cancer immunotherapy adjunct, and vaccine response enhancement have been published in international peer-reviewed journals.

Novelty: Low. Well-established compound with decades of research and clinical use.

Effect size: Moderate in hepatitis B (improvement in virologic response rates when combined with interferon or nucleoside analogs). Modest as a cancer immunotherapy adjunct. The effect size in immune reconstitution is well characterized but not transformative.

Promising potential: Moderate. Established clinical product with defined indications. Development trajectory is mature; major new indications are unlikely.

Side-effect profile: Favorable. Well characterized in international clinical trials. Principal adverse events are injection-site reactions. No serious systemic toxicity.

Overall validation: High. The most validated thymic peptide by international regulatory standards.

Comparison to Vilon: Thymosin alpha-1 and Vilon operate through fundamentally different mechanisms (receptor-mediated Toll-like receptor signaling versus epigenetic chromatin remodeling) and target different aspects of immune function. Thymosin alpha-1 has vastly greater international clinical validation and regulatory acceptance. Vilon has the potential advantage of the epigenetic mechanism, which may produce broader and more durable effects on age-related immune decline through reactivation of silenced genes rather than through transient receptor stimulation. The compounds are mechanistically complementary and could in principle be combined for synergistic immunomodulation.

12.4 Thymulin (FTS, facteur thymique serique)

Mechanism: A nonapeptide (Glu-Ala-Lys-Ser-Gln-Gly-Gly-Ser-Asn) originally isolated from porcine thymic serum by Bach and Dardenne. Thymulin requires zinc for biological activity and acts through a specific high-affinity receptor on T-lymphocytes to promote T-cell differentiation and function. The mechanism includes modulation of T-cell cytokine production, promotion of T-cell precursor differentiation, and anti-inflammatory effects through suppression of proinflammatory cytokines [23, 24].

Development trajectory: Thymulin has been extensively characterized in pre-clinical models and in small clinical studies for immune modulation, anti-aging, and neuroprotection. It has not achieved pharmaceutical registration in any major jurisdiction. The zinc-dependent biological activity introduces a complexity (zinc bioavailability as a determinant of thymulin function) that has complicated development.

Novelty: Moderate. The zinc-dependent mechanism is distinctive within the thymic peptide class.

Effect size: Moderate in preclinical immune modulation models. Clinical evidence is limited to small studies.

Promising potential: Low to moderate. No commercial development pathway. Research tool with ongoing academic interest.

Side-effect profile: Favorable in published studies. No systematic safety concerns.

Overall validation: Low to moderate. Extensive preclinical literature; limited clinical validation.

Comparison to Vilon: Thymulin and Vilon are both thymus-derived peptides with immunomodulatory activity, but they differ in size (nonapeptide versus dipeptide), mechanism (receptor-mediated versus epigenetic), and zinc dependence (thymulin requires zinc; Vilon does not). Vilon has the advantage of simpler synthesis, lower cost, and the specific geroprotective evidence. Thymulin has the advantage of a well-characterized receptor and a more extensive international preclinical literature.

12.5 Epithalon (AEDG; Ala-Glu-Asp-Gly)

Mechanism: Synthetic tetrapeptide bioregulator of pineal origin, derived from the polypeptide extract Epithalamin. Epithalon is the most studied Khavinson peptide and the compound that drove international interest in the bioregulatory peptide class. The mechanism includes activation of telomerase in human somatic cells, regulation of melatonin synthesis, and geroprotective effects through composite anti-aging pathways [14, 15, 25].

Development trajectory: Epithalon has been studied in extensive preclinical lifespan studies (SHR mice, Drosophila, rats) with consistent geroprotective effects including increased mean lifespan, decreased tumor incidence, and telomerase activation. Clinical data from the Khavinson group include the geriatric mortality cohort studies and observational data from use in Russia. The compound has not achieved pharmaceutical registration in any jurisdiction and is available as a research-grade peptide.

Novelty: Moderate to high. The telomerase activation mechanism distinguishes Epithalon from other Khavinson peptides and from other geroprotective compounds.

Effect size: Substantial in preclinical lifespan studies (20 to 40 percent increase in mean lifespan in some models). Clinical effect size on mortality in observational cohorts is notable but uncontrolled.

Promising potential: Moderate. Strong preclinical data; absent international clinical validation. Substantial longevity-community interest.

Side-effect profile: Favorable. No consistent adverse events in published preclinical or clinical data.

Overall validation: Moderate. The most validated Khavinson peptide by volume of preclinical data, but limited by the same clinical evidence limitations (single research network, observational design) that affect all Khavinson peptides.

Comparison to Vilon: Epithalon and Vilon are complementary Khavinson peptides, targeting different organ systems (pineal versus thymus) and different molecular targets (telomerase activation versus immune chromatin remodeling). The combination has been studied in the geriatric mortality cohort (Thymalin plus Epithalamin produced the greatest mortality reduction) and represents the conceptual core of the Khavinson geroprotective protocol. Vilon has the advantage of thymic-specific immunomodulatory effects; Epithalon has the advantage of the telomerase mechanism and the broader preclinical lifespan evidence base.

12.6 Comparator summary

The five comparators span the thymic and immunomodulatory peptide space from defined chemical entities (Thymogen, Thymosin alpha-1, Thymulin, Epithalon) to complex tissue extracts (Thymalin). **Thymosin alpha-1** has the greatest international clinical and regulatory validation, with approval in more than 35 countries and published randomized controlled trials in hepatitis B and cancer immunotherapy. **Thymalin** has the longest clinical history within the Khavinson system and the strongest observational mortality data. **Thymogen** is the sister dipeptide with pharmaceutical registration in the Russian Federation. **Thymulin** represents a mechanistically distinct (zinc-dependent, receptor-mediated) approach to thymic immunomodulation with limited clinical development. **Epithalon** is the complementary pineal geroprotective peptide with the strongest preclinical lifespan data in the Khavinson class.

Vilon occupies a distinctive niche in this landscape as the shortest bioactive immunomodulatory peptide characterized, the only Khavinson thymic dipeptide with specific geroprotective lifespan data in mammals, the only compound in the panel with the deheterochromatinization mechanism as its primary mode of action, and the compound with the most detailed molecular characterization of peptide-DNA interaction through the TCGA binding motif. Its principal limitations are the small and methodologically constrained clinical evidence base, the absence of international regulatory recognition, and the concentration of the research literature in a single investigator network. Investigators considering Vilon for immunomodulatory or geroprotective research should situate it within the broader comparative landscape and should consider the substantially greater clinical validation of Thymosin alpha-1 for indications where regulatory-grade evidence is required.

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