

RESEARCH MONOGRAPH . COMPOUND PROFILE

Pancragen

A synthetic tetrapeptide (Lys-Glu-Asp-Trp) developed at the Saint Petersburg Institute of Bioregulation and Gerontology as a tissue-specific epigenetic modulator of pancreatic cell differentiation, glucose homeostasis, and beta cell functional recovery in aging and type 2 diabetes mellitus.

DOCUMENT	KDC-MN-1403
ISSUED	2026-05-10
REVISION	1.0
AUTHOR	Kodiac bioLabs Research
COMPOUND CLASS	Synthetic tetrapeptide bioregulator of pancreatic endocrine and exocrine cell differentiation and function

ABSTRACT

Pancragen (Lys-Glu-Asp-Trp-NH₂; KEDW) is a synthetic tetrapeptide bioregulator developed by Vladimir Khavinson and colleagues at the Saint Petersburg Institute of Bioregulation and Gerontology (Russia) as a tissue-specific modulator of pancreatic endocrine and exocrine cell differentiation and function. The compound belongs to the Khavinson class of ultrashort (two to four amino acid) bioregulatory peptides, a pharmacological category defined by the hypothesis that short peptides penetrate cell nuclei, bind complementary DNA sequences in promoter regions through electrostatic and hydrogen-bond interactions, and modulate gene expression in a tissue-specific manner without engaging classical cell-surface receptors. Pancragen was derived from fractionation of bovine pancreatic tissue extracts; the tetrapeptide Lys-Glu-Asp-Trp was identified as the minimal active sequence responsible for the pancreotrophic activity of the parent extract preparation Suprefort. The compound has a molecular formula of C₂₆H₃₆N₆O₉ (free acid form) and a molecular weight of 576.60 g/mol. Physical-chemical characterization by ultraviolet-visible absorption spectroscopy, circular dichroism, and molecular modeling has demonstrated that the KEDW tetrapeptide binds double-stranded DNA in the major groove at sequences containing the ACCT motif, which is found in promoter regions of genes responsible for pancreatic cell differentiation and function [1]. The principal downstream molecular consequence of this interaction is upregulation of transcription factors that govern pancreatic endocrine cell fate, including PDX1 (the earliest marker of pancreatic progenitor cells and the master regulator of beta cell identity), NGN3, PAX6, PAX4, FOXA2, NKX2-2, and

NKX6.1 [2, 3]. In organotypic pancreatic cell cultures from young and aged rats, Pancragen stimulated the expression of differentiation factors of both acinar cells (Pdx1, Ptf1a) and islet of Langerhans cells (Pdx1, Pax6, Pax4, Foxa2, Nkx2.2), with the inducing effect more pronounced in aged cultures, consistent with a geroprotective mechanism [3]. Preclinical pharmacology in streptozotocin-induced diabetic rats demonstrated that oral Pancragen produced a pronounced hypoglycemic effect during the treatment period and that intramuscular administration normalized the adhesion properties of mesenteric capillary endothelium without modifying capillary permeability, suggesting homeostatic and endothelioprotective activity in early diabetes [4]. In a study of biological activity using immunoenzyme and high-performance liquid chromatography methods, the tetrapeptide modulated metabolic parameters characterizing apoptosis, including caspase-3 activity, in pancreatic beta cells and hepatocytes from streptozotocin-treated animals [5]. Primate studies in aged female rhesus monkeys demonstrated that a 10-day intramuscular course of Pancragen at 50 micrograms per day markedly increased the glucose disappearance rate, decreased basal insulin and C-peptide levels, and normalized glucose, insulin, and C-peptide dynamics during intravenous glucose tolerance testing, with partial persistence of these effects for three weeks after cessation of treatment [6, 7]. A comparative study in the same primate model demonstrated that Pancragen normalized insulin and C-peptide levels (suggesting recovery of disturbed glucose tolerance) while glimepiride produced a stronger but delayed blood-glucose-lowering effect without substantially affecting insulin secretion, indicating mechanistically distinct activity [7]. In a clinical study of 33 elderly patients with type 2 diabetes mellitus, Pancragen administered against a background

of constant-dose glibenclamide significantly decreased fasting plasma glucose and glucose concentrations at two hours during oral glucose tolerance testing, reduced plasma insulin levels, and decreased the HOMA insulin resistance index; an additional glucose-lowering effect persisted for two weeks after cessation of Pancragen in 60 percent of patients who continued glibenclamide at unchanged doses [8]. Organotypic tissue culture studies confirmed that Pancragen at concentrations as low as 0.05 ng/mL stimulated tissue growth in pancreatic explants from both young and aged rats, with the stimulating effect tissue-specific (no effect on non-pancreatic tissue explants at the same concentration) [9]. The compound has not been approved by the United States Food and Drug Administration, the European Medicines Agency, or any major Western regulatory authority. It is marketed in Russia as a dietary supplement (Pancragen capsules) and is available internationally as a research-grade peptide from multiple suppliers. Formal toxicology studies meeting International Council for Harmonisation or FDA regulatory standards have not been published. The existing safety data, derived exclusively from the Khavinson research network, report no significant adverse events in preclinical or clinical studies at the doses and durations studied. This monograph reviews the chemistry, synthesis, and structural class of Pancragen; the epigenetic and transcriptional mechanism of action; the available pharmacokinetic considerations for ultrashort peptides; the preclinical pharmacology in cell culture, rodent, and primate models; the clinical evidence base in type 2 diabetes; sourcing and quality verification; reconstitution and handling; stack interactions; adverse events and safety signals; and a comparative assessment of five alternative pancreatic bioregulatory or beta cell-active compounds against Pancragen on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Common name: Pancragen.

Systematic peptide name: Lys-Glu-Asp-Trp-NH₂ (one-letter code: KEDW-NH₂). The C-terminal amide is the standard synthetic form; the free-acid form (Lys-Glu-Asp-Trp-OH) has been used in some biophysical studies but is not the formulated material.

Development designation: Pancragen is the proprietary name assigned by the Saint Petersburg Institute of Bioregulation and Gerontology. The compound is also referenced in the literature as "tetrapeptide KEDW" and as "pancreatic bioregulator peptide" in the context of the broader Khavinson bioregulatory peptide class.

Chemical Abstracts Service registry number: Not assigned in the Chemical Abstracts Service registry at the time of monograph preparation. The compound is catalogued by peptide research suppliers under proprietary catalog numbers.

International Union of Pure and Applied Chemistry name: L-lysyl-L-alpha-glutamyl-L-alpha-aspartyl-L-tryptophanamide.

Marketed name: Pancragen (Saint Petersburg Institute of Bioregulation and Gerontology; marketed in Russia as a dietary supplement in capsule form).

1.2 Structural class and chemistry

Pancragen is a linear, unbranched tetrapeptide composed of four L-amino acid residues (lysine, glutamic acid, aspartic acid, tryptophan) with a C-terminal primary amide. The structural class is the Khavinson bioregulatory peptide family, a defined set of ultrashort (two to four amino acid) synthetic peptides each designed to recapitulate the tissue-specific bioactivity of a parent organ-derived peptide extract [10].

Molecular formula: C₂₆H₃₆N₆O₉ (free acid form); C₂₆H₃₇N₇O₈ (C-terminal amide form, the standard synthetic product).

Molecular weight: 576.60 g/mol (free acid); 575.62 g/mol (amide).

Physical properties: White to off-white lyophilized powder. Freely soluble in water and in aqueous buffers at physiological pH. Soluble in dimethyl sulfoxide. Sparingly soluble in neat organic solvents (ethanol, methanol). The compound is hygroscopic in lyophilized form and should be stored desiccated.

Stereochemistry: All four residues are in the L-configuration. Racemization at any position would abolish the tissue-specific DNA-binding activity and is a quality-control concern for research-grade material. Enantiomeric purity should be confirmed by chiral chromatography or by comparison of circular dichroism spectra to a reference standard.

Charge state at physiological pH: The peptide carries a net charge of approximately minus one at pH 7.4: the lysine epsilon-amino group is protonated (positive), the glutamic acid and aspartic acid side-chain carboxylates are deprotonated (two negative charges), and the N-terminal alpha-amino group is protonated (positive), yielding a net charge of approximately zero to minus one depending on the precise microenvironment. The overall acidic character contributes to the major-groove DNA binding through electrostatic complementarity with the phosphodiester backbone.

1.3 Synthesis

Pancragen is synthesized by standard solid-phase peptide synthesis (Fmoc chemistry) on Rink amide resin to generate the C-terminal amide. The synthesis proceeds from C-terminus to N-terminus: Fmoc-Trp(Boc)-OH is coupled to the resin, followed by sequential deprotection and coupling of Fmoc-Asp(OtBu)-OH, Fmoc-Glu(OtBu)-OH, and Fmoc-Lys(Boc)-OH. Side-chain protecting groups (tert-butyl esters for Asp and Glu, tert-butyloxycarbonyl for Lys and Trp indole nitrogen) are removed simultaneously with resin cleavage using trifluoroacetic acid with appropriate scavengers (triisopropylsilane, water, 1,2-ethanedithiol). The crude peptide is purified by reverse-phase high-performance liquid chromatography (C18 column, acetonitrile-water gradient with 0.1 percent trifluoroacetic acid modifier) and lyophilized. Identity is confirmed by electrospray ionization mass spectrometry or matrix-assisted laser desorption ionization time-of-flight mass spectrometry; purity is assessed by analytical reverse-phase high-performance liquid chromatography at 220 nm. Research-grade material is supplied at greater than 95 percent pu-

rity; pharmaceutical-research-grade preparations target greater than 98 percent purity. The synthesis is straightforward, with no unusual coupling difficulties, and gram-scale production is routine for commercial peptide suppliers.

2. Abstract

Pancragen (Lys-Glu-Asp-Trp-NH₂; KEDW) is a synthetic tetrapeptide bioregulator developed by Khavinson and colleagues at the Saint Petersburg Institute of Bioregulation and Gerontology as a tissue-specific epigenetic modulator of pancreatic cell differentiation and function [1, 2, 3]. The compound belongs to the Khavinson class of ultrashort bioregulatory peptides, a pharmacological category hypothesized to operate through direct peptide-DNA interaction in the cell nucleus rather than through classical receptor-mediated signaling. Physical-chemical studies using ultraviolet-visible spectroscopy, circular dichroism, and molecular modeling have demonstrated that the KEDW sequence binds double-stranded DNA in the major groove at sites containing the ACCT motif, which is present in promoter regions of genes governing pancreatic endocrine and exocrine cell fate [1].

The principal molecular consequence of Pancragen-DNA interaction is upregulation of transcription factors critical to pancreatic beta cell identity and function: PDX1 (pancreatic and duodenal homeobox 1, the master regulator of beta cell development and insulin gene transcription), NGN3 (neurogenin-3, required for endocrine progenitor specification), PAX6, PAX4, FOXA2, NKX2-2, and NKX6.1 [2, 3]. In organotypic pancreatic cell cultures, Pancragen stimulated differentiation of both acinar cells and islet of Langerhans cells, with the effect more pronounced in aged cultures, suggesting a mechanism for restoration of age-depleted pancreatic cell populations [3]. The differentiation of pancreatic cells induced by Pancragen has been proposed as the mechanism underlying both its anti-diabetic and anti-inflammatory effects [3].

Preclinical pharmacology spans three model systems. In streptozotocin-induced diabetic rats, oral Pancragen produced a pronounced hypoglycemic effect during the treatment period, and intramuscular administration normalized endothelial adhesion properties in mesenteric capillaries [4]. In aged female rhesus monkeys with impaired glucose tolerance, a 10-day intramuscular course of Pancragen at 50 micrograms per day increased the glucose disappearance rate, normalized insulin and C-peptide dynamics, and produced effects that persisted partially for three weeks after treatment cessation [6, 7]. A comparative primate study demonstrated

mechanistic distinction from glimepiride: Pancragen normalized insulin secretory dynamics while glimepiride produced a stronger acute glucose-lowering effect without restoring the insulin secretion pattern [7].

The sole published clinical study evaluated Pancragen in 33 elderly patients with type 2 diabetes mellitus on background glibenclamide therapy [8]. Pancragen significantly reduced fasting plasma glucose, improved oral glucose tolerance test results at two hours, decreased plasma insulin concentrations, and reduced the HOMA insulin resistance index. An additional glucose-lowering effect persisted for two weeks after Pancragen discontinuation in 60 percent of patients continuing glibenclamide at unchanged doses. The persistence of effect beyond the treatment period is consistent with an epigenetic or differentiation-based mechanism rather than a simple pharmacodynamic effect that terminates with drug clearance.

The compound has not been approved by the United States Food and Drug Administration, the European Medicines Agency, or any other Western regulatory authority. It is marketed in Russia as a dietary supplement and is available internationally as a research-grade peptide. Formal regulatory-standard toxicology studies have not been published. The compound is not in active pharmaceutical development for any indication outside the Khavinson research network.

This monograph reviews the chemistry, synthesis, epigenetic mechanism of action, pharmacokinetic considerations, preclinical and clinical pharmacology, sourcing and quality verification, reconstitution and handling, stack interactions, adverse events and safety signals, and a comparative assessment of five alternative compounds against Pancragen on five competency standards.

3. Discovery and Development History

3.1 Origin of the bioregulatory peptide concept

The bioregulatory peptide program at the Saint Petersburg Institute of Bioregulation and Gerontology (formerly the Bioregulation and Gerontology Research Institute of the Russian Academy of Medical Sciences) was initiated by Vladimir Khavinson in the 1970s and 1980s. The foundational hypothesis was that each organ system produces endogenous short peptides that regulate gene expression in a tissue-specific manner and that these peptides decline with aging, contributing to age-related organ dysfunction [10]. The initial research program involved extraction, fractionation, and characterization of peptide complexes from bovine organ preparations (thymus, pineal gland, prostate, bronchial tissue, cardiac tissue, pancreas, and others), followed by identification of the minimal active peptide sequence responsible for the tissue-specific activity, and finally synthesis of the identified sequence for standardized pharmacological and clinical study.

3.2 Isolation of the pancreatic bioregulator

The pancreatic bioregulatory peptide was first isolated as a complex extract from bovine pancreatic tissue, designated Suprefort (also known as A-1 Pancreas Peptide Bioregulator). Suprefort is a nucleoprotein complex containing multiple peptide species; it was characterized in preclinical studies as normalizing pancreatic enzyme activity, improving glucose metabolism, and supporting pancreatic tissue regeneration in aging and chronic pancreatitis models [11]. The synthetic analog program sought to identify the minimal active peptide sequence within the Suprefort complex. Through systematic fractionation and activity-guided selection, the tetrapeptide Lys-Glu-Asp-Trp was identified as the principal pancreotropic sequence and was designated Pancragen [10].

3.3 Characterization of DNA-binding mechanism

The molecular mechanism of Pancragen was characterized in a 2015 publication by Khavinson, Tendler, Kasyanenko, and Tarnovskaya, who used ultraviolet-visible absorption spectroscopy, circular dichroism spectroscopy, and computational molec-

ular modeling to demonstrate that the KEDW tetrapeptide binds double-stranded DNA in the major groove [1]. The binding was shown to be sequence-preferential, with the peptide associating with DNA at sites containing the ACCT motif. This motif is found in promoter regions of genes responsible for pancreatic cell differentiation, including PDX1, providing a molecular basis for the tissue-specific gene-regulatory activity. The study produced a three-dimensional model of the stable DNA-peptide complex through molecular dynamics simulation.

3.4 Expansion of the preclinical and clinical evidence

Between 2006 and 2017, the Khavinson laboratory and collaborators published a series of studies extending the characterization of Pancragen from in vitro organotypic cultures through rodent models and primate models to a limited clinical study. The organotypic culture work (Zakutskii et al. 2006) demonstrated tissue-specific stimulation of pancreatic explant growth at concentrations of 0.05 ng/mL [9]. The streptozotocin rat study (Khavinson et al. 2007) demonstrated the hypoglycemic and endothelioprotective effects [4]. The differentiation study (Khavinson et al. 2013) characterized the transcription-factor expression profile [3]. The primate studies (Goncharova et al. 2014, 2015) extended efficacy to aged rhesus monkeys and compared Pancragen to glimepiride [6, 7]. The clinical study (Korkushko et al. 2011) provided the first human evidence of glucose-lowering and insulin-sensitizing activity [8].

3.5 Current development status

Pancragen is not in active pharmaceutical development for any indication outside the Khavinson research network. The compound is marketed in Russia as a dietary supplement (Pancragen capsules) through the NPCRIZ/Peptide Bio distribution network and is available internationally through peptide research suppliers. No Phase 2 or Phase 3 clinical trials meeting International Council for Harmonisation standards have been conducted or registered in Western clinical trial databases. The current research-clinical state is one of tissue-culture-through-primate preclinical support, a single small clinical study in elderly diabetic patients, a plausible epigenetic mechanism, and absent Western regulatory validation.

4. Mechanism of Action

4.1 Epigenetic gene regulation through direct DNA binding

The proposed mechanism of action of Pancragen is fundamentally distinct from conventional peptide pharmacology. Rather than binding cell-surface receptors to initiate signal transduction cascades, Khavinson bioregulatory peptides are hypothesized to penetrate cell membranes and nuclear membranes, enter the cell nucleus, and bind directly to specific DNA sequences in promoter regions to modulate gene transcription [1, 10]. This hypothesis is supported by fluorescence microscopy studies on related Khavinson peptides (notably Epitalon) demonstrating nuclear localization, and by physical-chemical studies on Pancragen itself demonstrating DNA binding *in vitro*.

Khavinson, Tendler, Kasyanenko, and Tarnovskaya (2015) characterized the KEDW-DNA interaction using three complementary approaches [1]. Ultraviolet-visible absorption spectroscopy demonstrated changes in the DNA absorption spectrum upon addition of KEDW consistent with major-groove binding. Circular dichroism spectroscopy showed perturbation of the B-form DNA signal upon peptide addition, further supporting a groove-binding mode rather than intercalation. Molecular modeling using molecular dynamics simulation produced a three-dimensional model of the KEDW-DNA complex in which the peptide sits in the major groove and makes specific contacts with the ACCT sequence motif through a combination of electrostatic interactions (lysine epsilon-amino group with the phosphodiester backbone; glutamic acid and aspartic acid carboxylates with exposed base functional groups) and hydrogen bonds (tryptophan indole nitrogen with thymine carbonyl oxygen in the major groove).

The ACCT motif targeted by KEDW is found in the promoter regions of several genes critical to pancreatic cell differentiation and function, providing a molecular basis for tissue-specific gene regulation [1].

4.2 Transcription factor upregulation in pancreatic cells

The downstream consequence of KEDW-DNA interaction is modulation of transcription factor expression in pancreatic cells. Khavinson et al. (2013) demonstrated in organotypic pancreatic cell cultures from young (3-month) and aged (24-month) rats that Pancragen stimulated the expression of the following transcription factors [3]:

Acinar cell differentiation factors: Pdx1 (pancreatic and duodenal homeobox 1), Ptf1a (pancreas-specific transcription factor 1a). Both are essential for acinar cell identity and exocrine pancreatic function.

Islet of Langerhans differentiation factors: Pdx1, Pax6 (paired box 6), Pax4 (paired box 4), Foxa2 (forkhead box A2), Nkx2.2 (NK2 homeobox 2). These transcription factors collectively govern endocrine progenitor specification, beta cell commitment, and mature beta cell function including insulin gene transcription.

The inducing effect was more pronounced in aged cultures than in young cultures, consistent with the geroprotective hypothesis: age-related decline in endogenous bioregulatory peptide levels results in decreased transcription factor expression and impaired cell differentiation, and exogenous supplementation with the synthetic peptide restores the expression pattern toward youthful levels [3].

Additional gene expression studies demonstrated that KEDW increased expression of NGN3 (neurogenin-3, required for endocrine progenitor specification from ductal progenitor cells), NKX6.1 (essential for beta cell maturation and insulin secretion competence), while decreasing expression of MNX1 and HOXA3 [2].

4.3 PDX1 as the central effector

PDX1 upregulation by Pancragen is of particular mechanistic significance. PDX1 is the earliest marker of pancreatic progenitor cells during embryonic development, is required for both endocrine and exocrine pancreatic specification, and in the adult pancreas functions as the master regulator of beta cell identity, insulin gene transcription, glucose sensing through glucokinase expression, and beta cell survival [12]. Loss of PDX1 expression in adult beta cells causes dedifferentiation and loss of glucose-stimulated insulin secretion. Age-related decline in PDX1 expression has been documented in both rodent and human pancreatic islets and is implicated in age-related glucose intolerance and type 2 diabetes risk [13].

The ability of Pancragen to upregulate PDX1 expression in aged pancreatic cells provides a mechanistic link between the epigenetic DNA-binding activity at the molecular level and the functional pancreatic recovery observed in preclinical and clinical studies.

4.4 Anti-apoptotic activity

Khavinson et al. (2010) demonstrated that the KEDW tetrapeptide modulated metabolic parameters characterizing apoptosis in pancreatic beta cells and hepatocytes from streptozotocin-treated animals [5]. The study used immunoenzyme and high-performance liquid chromatography methods to assess caspase-3 activity and other apoptotic markers. Pancragen reduced caspase-3 activity in beta cells, suggesting a cytoprotective mechanism that complements the differentiation-promoting activity. The anti-apoptotic effect may contribute to preservation of beta cell mass in aging and in early diabetes.

4.5 Endothelioprotective activity

In streptozotocin-induced diabetic rats, intramuscular Pancragen normalized the adhesion properties of mesenteric capillary endothelium without modifying capillary permeability [4]. The mechanism of this vascular effect is not fully characterized but may involve indirect consequences of improved pancreatic endocrine function (reduced hyperglycemia-driven endothelial activation) or direct peptide effects on endothelial gene expression through the same DNA-binding mechanism operating in vascular cells.

4.6 Mechanistic context and controversy

The Khavinson epigenetic peptide hypothesis is supported by a substantial publication record (over 800 papers from the Khavinson laboratory and collaborators) and by biophysical characterization of peptide-DNA interactions for multiple members of the class [10]. However, the mechanism remains controversial in Western pharmacology for several reasons: (a) the proposal that tetrapeptides penetrate intact cell membranes, nuclear membranes, and histones to access promoter DNA in chromatin is not supported by independent replication outside the Khavinson network; (b) the binding affinities reported for peptide-DNA complexes in cell-free systems may not translate to the chromatin environment where DNA is complexed with histones and other proteins; (c) the gene-expression changes observed in cell

culture may reflect indirect effects through conventional signaling pathways rather than direct DNA binding; and (d) the research has been conducted almost exclusively within a single laboratory network without independent Western replication of the key mechanistic experiments. Investigators should interpret the mechanistic data with appropriate consideration of these limitations.

5. Pharmacokinetics and Routes of Administration

5.1 General considerations for ultrashort peptides

Formal pharmacokinetic studies of Pancragen (absorption, distribution, metabolism, elimination parameters; plasma concentration-time curves; absolute bioavailability determination) have not been published. The pharmacokinetic profile of Pancragen must therefore be inferred from general principles of ultrashort peptide pharmacology and from the limited data available on the Khavinson bioregulatory peptide class as a whole.

Ultrashort peptides (two to four amino acids) occupy a unique pharmacokinetic niche relative to larger peptide therapeutics. Their small molecular size (typically less than 600 daltons) places them below the conventional molecular weight cutoff for passive transcellular absorption in the gastrointestinal tract. Di- and tripeptides are substrates of the intestinal peptide transporter PepT1 (SLC15A1), which mediates active absorption of dietary protein digestion products and of peptidomimetic drugs (beta-lactam antibiotics, angiotensin-converting enzyme inhibitors). Tetrapeptides are not classical PepT1 substrates but may be absorbed through a combination of passive paracellular transport, transcellular diffusion, and partial hydrolysis to di- and tripeptide fragments that are then PepT1-transported [14].

5.2 Oral absorption

The Khavinson group has advanced oral Pancragen administration as a viable route, and the clinical study of Korkushko et al. (2011) used oral administration [8]. The rat study of Khavinson et al. (2007) demonstrated a pronounced hypoglycemic effect with oral Pancragen, confirming that the compound reaches systemic circulation and exerts biological activity after oral dosing [4]. However, the absolute oral bioavailability (the fraction of the administered dose reaching the systemic circulation as intact tetrapeptide) has not been quantified.

The Khavinson group has argued that the ultrashort length of bioregulatory peptides confers resistance to gastrointestinal proteolytic degradation: dipeptidyl peptidases, aminopeptidases, and endopeptidases that rapidly cleave larger peptides have diminished activity on substrates shorter than five residues [10]. This argument has biological plausibility but has not been validated with formal pharmacokinetic studies using radiolabeled or isotope-labeled Pancragen.

5.3 Distribution

The tissue distribution of Pancragen has not been characterized by formal radiolabel or mass-spectrometric tissue-distribution studies. The tissue-specific activity observed in organotypic culture experiments (stimulation of pancreatic tissue growth with no effect on non-pancreatic tissue at the same concentration) suggests preferential activity in pancreatic cells, though this could reflect tissue-specific gene-expression responsiveness rather than tissue-specific accumulation [9].

The proposed mechanism requires nuclear entry, implying that the peptide must cross the plasma membrane, traverse the cytoplasm, and enter the nucleus. The Khavinson group has demonstrated nuclear localization of fluorescently labeled short peptides (including Epitalon) by confocal microscopy, supporting the plausibility of this distribution pathway for the class [10].

5.4 Metabolism and elimination

Tetrapeptides in plasma are subject to rapid degradation by serum peptidases, with expected plasma half-lives on the order of minutes to low tens of minutes for unmodified linear peptides. The C-terminal amide on Pancragen provides modest protection against carboxypeptidase-mediated degradation but does not protect against aminopeptidase or endopeptidase cleavage. Metabolic products would be individual amino acids (lysine, glutamic acid, aspartic acid, tryptophan) entering endogenous amino acid pools; no pharmacologically active metabolites are expected.

The short expected plasma residence time of the intact peptide raises a pharmacokinetic paradox: the persistence of biological effects for weeks after a 10-day treatment course (observed in both the primate and clinical studies) [6, 7, 8] is not consistent with the pharmacokinetics of a rapidly degraded peptide. The Khavinson group resolves this paradox by invoking the epigenetic mechanism: the

peptide triggers gene-expression changes (chromatin remodeling, transcription factor upregulation) that persist after the peptide itself is cleared, analogous to the hit-and-run kinetics of epigenetic drugs such as DNA methyltransferase inhibitors [10].

5.5 Routes of administration

Three routes have been used in published studies: oral (capsule, the clinical study and one arm of the rat study), intramuscular injection (the primate studies and one arm of the rat study), and addition to cell culture medium (the in vitro studies). Subcutaneous injection is used in research-grade protocols but has not been characterized in published pharmacological studies. The oral route is the most clinically relevant and is the marketed formulation.

6. Preclinical Pharmacology

6.1 Organotypic tissue culture studies

Zakutskii et al. (2006) evaluated four synthetic bioregulatory peptides (cardiogen, bronchogen, prostamax, and Pancragen) in organotypic tissue cultures from young (3-week) and aged (18-month) rats [9]. Pancragen at a concentration of 0.05 ng/mL stimulated the growth of pancreatic tissue explants compared to control explants in all age groups. The stimulating effect was tissue-specific: Pancragen stimulated pancreatic explants but not cardiac, pulmonary, or prostatic explants at the same concentration, while each of the other peptides stimulated its cognate tissue but not non-cognate tissues. This study established the tissue-specific bioactivity of Pancragen at very low concentrations and confirmed the principle of organ-specific peptide bioregulation.

6.2 Pancreatic cell differentiation in aging

Khavinson et al. (2013) characterized the effects of Pancragen on the differentiation of pancreatic cells during aging using organotypic cultures of pancreatic tissue from young and aged rats [3]. Expression of differentiation markers was found to be reduced during aging of pancreatic cells. Pancragen stimulated the expression of differentiation factors of acinar cells (Pdx1, Ptf1a) and islet of Langerhans cells (Pdx1, Pax6, Pax4, Foxa2, Nkx2.2) in both young and aged cultures, with the effect more pronounced in aged cultures. The authors concluded that differentiation of acinar and islet pancreatic cells induced by Pancragen can be a mechanism underlying its anti-diabetic and anti-inflammatory effects and that the transcription factors regulating differentiation of pancreatic cells represent a promising pharmacological target for treatment of diabetes mellitus and pancreatitis.

6.3 Streptozotocin-induced diabetes in rats

Khavinson et al. (2007) evaluated Pancragen in Wistar rats with streptozotocin-induced diabetes mellitus [4]. Two routes of administration were studied: oral and intramuscular. Oral Pancragen produced a pronounced hypoglycemic effect during the treatment period, confirming oral bioactivity. Intramuscular Pancragen nor-

malized the adhesion of mesenteric capillary endothelium but did not modify capillary permeability. The investigators concluded that Pancragen exhibited homeostatic and endothelioprotective effects during the initial phase of experimental diabetes.

6.4 Biological activity in streptozotocin models: apoptosis markers

Khavinson et al. (2010) studied the biological activity of Lys-Glu-Asp-Trp-NH₂ using immunoenzyme and high-performance liquid chromatography methods in streptozotocin-induced diabetes models [5]. The study evaluated the tetrapeptide's effects on metabolic parameters characterizing apoptosis, including caspase-3 activity, in insulin-producing pancreatic beta cells and in liver tissue. The results demonstrated modulation of apoptotic markers consistent with a cytoprotective effect, providing a mechanistic bridge between the transcription-factor upregulation observed *in vitro* and the functional pancreatic recovery observed in the intact animal.

6.5 Primate pharmacology: aged rhesus monkeys

Goncharova et al. (2014) investigated the impact of Pancragen on endocrine function of the pancreas in old female rhesus monkeys [6]. The study compared young adult and aged animals. Aged animals showed slower glucose clearance during intravenous glucose tolerance testing and elevated basal insulin and C-peptide levels compared to young animals, consistent with age-related insulin resistance and compensatory hyperinsulinemia. Following a 10-day intramuscular course of Pancragen at 50 micrograms per animal per day, the aged monkeys demonstrated markedly increased glucose disappearance rate, decreased basal insulin and C-peptide levels, and normalized glucose, insulin, and C-peptide dynamics during intravenous glucose tolerance testing. The beneficial effects persisted partially for three weeks after treatment cessation, consistent with an epigenetic mechanism producing effects that outlast the pharmacokinetic presence of the peptide.

Goncharova et al. (2015) extended this work to a comparative study of Pancragen versus glimepiride (a sulfonylurea insulin secretagogue) in the same aged primate model [7]. Nine elderly female rhesus monkeys received either Pancragen or glimepiride over 10 days. Pancragen normalized insulin and C-peptide levels, suggesting recovery of the disturbed glucose tolerance. Glimepiride produced a

stronger but delayed blood-glucose-lowering effect without substantially impacting the pattern of insulin secretion. The authors concluded that Pancragen is effective and safe for correction of age-related imbalance of endocrine pancreatic function and that its mechanism (normalization of insulin secretory dynamics) is distinct from that of sulfonylurea secretagogues (stimulation of insulin release without restoring the secretory pattern).

7. Clinical Evidence Base

7.1 Type 2 diabetes in elderly patients

The sole published clinical study of Pancragen was conducted by Korkushko, Khavinson, Shatilo, Antonyk-Sheglova, and Bondarenko and published in the Bulletin of Experimental Biology and Medicine in 2011 [8]. The study enrolled two groups of older individuals: 30 healthy subjects and 33 patients with type 2 diabetes mellitus. The study evaluated Pancragen administered orally against a background of constant-dose glibenclamide (a sulfonylurea).

Key findings in the diabetic cohort receiving Pancragen:

Fasting plasma glucose decreased significantly during the treatment period. Glucose concentrations at two hours during the oral glucose tolerance test decreased significantly. Plasma insulin levels decreased, suggesting improved insulin sensitivity rather than increased insulin secretion. The HOMA insulin resistance index decreased under the influence of Pancragen, confirming improved insulin sensitivity. Nocturnal melatonin levels, which were significantly reduced (by approximately 70 percent) in diabetic patients compared to age-matched healthy controls, were also measured as part of the study's assessment of neuroendocrine function.

An additional glucose-lowering effect persisted for two weeks after cessation of Pancragen treatment in 60 percent of patients who continued glibenclamide at unchanged doses. This persistence of effect is the most clinically notable finding and is consistent with the proposed epigenetic mechanism: if Pancragen induces durable changes in gene expression (upregulation of PDX1 and other beta cell transcription factors, improved beta cell differentiation state), the functional improvement would be expected to outlast the pharmacokinetic clearance of the peptide.

The control diabetic patients receiving no Pancragen showed no metabolic changes over the study period.

The authors concluded that Pancragen represents a promising approach to the correction of insulin resistance in elderly individuals.

7.2 Limitations of the clinical evidence

The clinical evidence for Pancragen is limited to a single study with 33 diabetic patients, conducted within the Khavinson research network and published in a Russian-origin journal (Bulletin of Experimental Biology and Medicine). The study was not registered in ClinicalTrials.gov or other Western clinical trial registries. The randomization and blinding procedures are not fully described in the available English-language abstract. The dose of Pancragen used in the clinical study is not clearly specified in the available English-language publications. No placebo-controlled arm independent of glibenclamide background therapy was included. No Western regulatory authority has reviewed the clinical data. Independent replication by investigators outside the Khavinson network has not been published.

Investigators should interpret the clinical evidence as preliminary and hypothesis-generating rather than as registration-quality clinical data.

8. Sourcing and Quality Verification

Research-grade Pancragen is available from multiple peptide research suppliers (Peptide Sciences, Limitless Life Nootropics, NovoPro Labs, Core Peptides, and others) as a lyophilized powder, typically at 10 to 50 milligram quantities per vial at greater than 95 percent purity by HPLC. The compound is also marketed in Russia as a dietary supplement in capsule form through the Peptide Bio and NPCRIZ distribution networks.

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

- Reverse-phase high-performance liquid chromatography area-percent purity, ideally greater than 98 percent for mechanistic studies requiring dose-response precision
- Electrospray ionization mass spectrometry or matrix-assisted laser desorption ionization time-of-flight mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ for the amide form: 576.27 Da)
- Amino acid analysis confirming the Lys:Glu:Asp:Trp ratio of 1:1:1:1
- Circular dichroism spectroscopy comparison to a reference spectrum to confirm correct stereochemistry (all L-amino acids)
- Residual solvent analysis by gas chromatography (common synthesis solvents: dimethylformamide, dichloromethane, trifluoroacetic acid, acetonitrile)
- Endotoxin testing (limulus amebocyte lysate assay) for any preparation intended for in vivo research use, with acceptance criterion of less than 0.25 endotoxin units per milliliter

The research-grade Pancragen market is small relative to more widely studied peptides (BPC-157, GHK-Cu, thymosin alpha-1), and independent analytical validation of vendor certificates of analysis is advisable. Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab) can provide independent confirmation of identity and purity.

The capsule form marketed in Russia typically contains 200 micrograms of the active tetrapeptide per capsule with excipients; capsule contents are not subject to pharmaceutical-grade manufacturing standards and should not be assumed equiv-

alent to research-grade lyophilized material for in vitro or in vivo research.

9. Reconstitution and Handling

Pancragen lyophilized powder is reconstituted by addition of sterile water for injection, bacteriostatic water (0.9 percent benzyl alcohol), or phosphate-buffered saline at the desired stock concentration. A stock concentration of 1 mg/mL (approximately 1.7 millimolar for the amide form) is convenient for serial dilution to working concentrations in cell culture or for dose calculation in animal studies. For subcutaneous or intramuscular injection in research animals, reconstitution in bacteriostatic water or sterile normal saline is appropriate.

Reconstitution procedure: Add the calculated volume of solvent to the vial containing lyophilized Pancragen. Allow the solvent to flow gently down the vial wall; do not inject the solvent directly onto the lyophilized cake. Swirl gently until the powder is fully dissolved. Do not vortex or shake vigorously, as this may cause foaming and peptide adsorption to the air-liquid interface. The resulting solution should be clear and colorless. Do not use if the solution appears cloudy, discolored, or contains visible particulates.

Storage of reconstituted solution: Refrigerate at 2 to 8 degrees Celsius. Use within 14 days if reconstituted in sterile water; use within 28 days if reconstituted in bacteriostatic water. Label the vial with the reconstitution date and concentration.

Storage of lyophilized powder: Store desiccated at minus 20 degrees Celsius or below for long-term stability (greater than 12 months). Short-term storage (weeks) at 2 to 8 degrees Celsius is acceptable. Protect from light and moisture. The peptide is hygroscopic; allow the vial to equilibrate to room temperature before opening to prevent moisture condensation on the powder.

Aliquoting: For experiments requiring repeated access to the stock solution, prepare single-use aliquots at the time of reconstitution to avoid repeated freeze-thaw cycles. Ultrashort peptides are generally stable through at least three freeze-thaw cycles, but aliquoting is preferred practice.

Compatibility: Pancragen is compatible with standard laboratory plasticware (polypropylene tubes and tips) and with glass vials. No significant adsorption to polypropylene or borosilicate glass has been reported at concentrations above 0.01

mg/mL. At very low concentrations (below 0.01 mg/mL), peptide adsorption to surfaces may become significant; addition of 0.1 percent bovine serum albumin or 0.01 percent polysorbate 20 to working solutions can mitigate surface adsorption.

10. Stack Interactions and Combinations

10.1 Sulfonylureas and other insulin secretagogues

The clinical study of Korkushko et al. (2011) administered Pancragen against a background of constant-dose glibenclamide [8]. The combination produced additive glucose-lowering effects. Investigators combining Pancragen with sulfonylureas (glibenclamide, glimepiride, glipizide) or with meglitinides (repaglinide, nateglinide) should monitor for additive hypoglycemia, particularly in elderly patients or in patients with impaired renal or hepatic function. The comparative primate study demonstrated that Pancragen and glimepiride operate through distinct mechanisms (Pancragen normalizes insulin secretory dynamics; glimepiride stimulates insulin release without restoring the secretory pattern), suggesting that the combination is pharmacologically rational but requires glucose monitoring [7].

10.2 Metformin

Metformin (the first-line oral antidiabetic agent in most guidelines) operates through reduction of hepatic glucose output, improvement of peripheral insulin sensitivity, and activation of AMP-activated protein kinase. The mechanism is distinct from and complementary to the proposed Pancragen mechanism (upregulation of beta cell transcription factors and improvement of beta cell differentiation state). No published study has evaluated the Pancragen-metformin combination. The theoretical interaction profile is additive glucose-lowering without specific pharmacokinetic interaction, as metformin is renally eliminated and is not a substrate of the peptidases that would degrade Pancragen.

10.3 GLP-1 receptor agonists and DPP-4 inhibitors

GLP-1 receptor agonists (semaglutide, liraglutide, tirzepatide) and DPP-4 inhibitors (sitagliptin, saxagliptin) enhance insulin secretion through the incretin axis. The mechanism is complementary to the proposed Pancragen mechanism. No published study has evaluated these combinations. Investigators should consider that

both GLP-1 receptor agonists and Pancragen have been reported to support beta cell survival and proliferation in preclinical models; additive trophic effects on beta cell mass are theoretically plausible but uncharacterized.

10.4 Other Khavinson bioregulatory peptides

Pancragen is sometimes used in combination with other Khavinson peptides in the Russian bioregulatory peptide tradition. The commercially available "Complex Diabetic" product combines Pancragen with Svetinorm (liver bioregulator peptide, Lys-Glu-Asp-Gly) and Vilon (immune bioregulator peptide, Lys-Glu). No published pharmacological study has characterized these combinations. The theoretical basis for the combination is organ-system complementarity (pancreatic, hepatic, and immune bioregulation) rather than receptor-level synergy.

10.5 Insulin

Exogenous insulin and Pancragen operate through entirely different mechanisms (direct glucose disposal versus beta cell transcription factor upregulation). The combination has not been studied. Investigators combining the two should monitor for additive hypoglycemia, particularly if Pancragen produces its reported insulin-sensitizing effect in the context of fixed-dose exogenous insulin.

10.6 Suprefort

Suprefort (the natural pancreatic peptide extract from which Pancragen was derived) and Pancragen share the same target tissue and overlapping mechanisms. The Khavinson distribution network recommends sequential use: a course of Pancragen followed by a maintenance course of Suprefort [11]. No published pharmacological study characterizes the concurrent or sequential combination.

11. Adverse Events and Safety Signal

11.1 Preclinical safety

No significant adverse events or treatment-related toxicity have been reported in the published preclinical studies of Pancragen. The streptozotocin rat study (Khavinson et al. 2007) [4], the primate studies (Goncharova et al. 2014, 2015) [6, 7], and the organotypic culture studies (Zakutskii et al. 2006, Khavinson et al. 2013) [9, 3] report no safety signals at the doses and durations studied. The primate study explicitly concluded that Pancragen is "effective and safe for correction of age-related imbalance of endocrine pancreatic function" [7].

11.2 Clinical safety

The clinical study of Korkushko et al. (2011) in 33 elderly diabetic patients did not report significant adverse events [8]. However, the available English-language abstract does not provide a detailed adverse-event tabulation, and the study was not powered or designed as a safety study.

11.3 Expected class effects

Based on general pharmacological principles and on reports from commercial use:

- Injection site reactions (redness, mild swelling, transient discomfort) are expected with subcutaneous or intramuscular administration, as with any peptide injection
- Mild gastrointestinal effects (transient nausea, changes in digestive comfort) may occur with oral capsule administration, particularly during the initial adjustment period as pancreatic enzyme activity is modulated
- Hypoglycemia is a theoretical risk when Pancragen is combined with insulin secretagogues or exogenous insulin, given the additive glucose-lowering effects observed in the clinical study
- Transient fatigue during initial treatment has been reported anecdotally

11.4 Limitations of safety data

All published safety data for Pancragen originate from the Khavinson research network. No formal toxicology studies meeting International Council for Harmonisation (ICH) or FDA regulatory standards have been published. No drug-drug interaction studies have been conducted. No carcinogenicity, genotoxicity, or reproductive toxicity studies meeting regulatory standards have been published. No long-term safety follow-up data (beyond the weeks to months reported in the published studies) are available.

The theoretical concern specific to the epigenetic mechanism is that modulation of transcription factor expression in pancreatic cells could, in principle, produce unintended effects on cell proliferation or differentiation. PDX1 overexpression has been associated with both beta cell hyperplasia and, in some contexts, with acinar cell metaplasia in transgenic models. Whether the transient, low-dose Pancragen-induced PDX1 upregulation observed in the published studies is sufficient to raise this concern is unknown.

Investigators should treat the safety profile of Pancragen as incompletely characterized and should apply standard preclinical safety assessment procedures to any research protocol.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative compounds against Pancragen, evaluated against five competency standards: novelty, effect size, promising potential (current state and trajectory), side-effect profile, and overall validation. The five comparators were selected to represent the principal pharmacological strategies for pancreatic beta cell protection, regeneration, or functional enhancement that share conceptual overlap with the Pancragen research thesis.

12.1 Suprefort (Pancreatic Peptide Extract)

Mechanism: Natural peptide complex extracted from bovine pancreatic tissue using Khavinson's patented extraction technology. Contains multiple peptide species including the KEDW sequence that was subsequently synthesized as Pancragen. Acts through the same proposed epigenetic mechanism as Pancragen but as a complex mixture rather than a single defined molecular entity [11].

Novelty: Low. Suprefort is the parent extract from which Pancragen was derived. The mechanism and concept are identical; Suprefort represents the first-generation preparation and Pancragen the refined, single-entity second generation.

Effect size: Comparable to Pancragen in the limited published data. Suprefort has been reported to normalize pancreatic enzyme activity, improve glucose metabolism, and support pancreatic tissue regeneration in aging and chronic pancreatitis. Effect sizes have not been quantified in formal clinical studies.

Promising potential: Low. Suprefort is a dietary supplement marketed through the Khavinson distribution network without regulatory approval in any Western jurisdiction. It is not in pharmaceutical development and has no registered clinical trials. As a complex mixture, it faces additional regulatory and standardization challenges compared to Pancragen.

Side-effect profile: No significant adverse effects reported in the available literature. As a natural peptide complex, batch-to-batch variability is a concern, and allergenic potential from bovine tissue proteins cannot be excluded.

Overall validation: Low. Limited published preclinical data. No formal clinical trials. The evidence base is primarily commercial and anecdotal rather than peer-reviewed.

Comparison to Pancragen: Pancragen is the defined, synthetic, single-entity version of the Suprefort active principle. Pancragen has superior batch-to-batch reproducibility, defined molecular identity amenable to quality control, and a somewhat larger peer-reviewed evidence base. For research applications, Pancragen is preferred as the characterized, defined compound.

12.2 GLP-1 Receptor Agonists (Semaglutide as Representative)

Mechanism: Synthetic analogs of glucagon-like peptide-1 that activate the GLP-1 receptor on pancreatic beta cells, potentiating glucose-dependent insulin secretion, suppressing glucagon release, slowing gastric emptying, and promoting satiety. Semaglutide additionally has demonstrated cardiovascular and renal protective effects in large outcomes trials [15].

Novelty: Low for the class (incretin-based therapy has been established for over 15 years), though tirzepatide (dual GIP/GLP-1 agonist) represents continued mechanistic innovation within the class.

Effect size: Large. GLP-1 receptor agonists produce HbA1c reductions of 1.0 to 2.0 percent, body weight reductions of 5 to 15 percent (semaglutide 2.4 mg), and cardiovascular risk reduction in dedicated outcomes trials. The effect size substantially exceeds any reported for Pancragen or other bioregulatory peptides.

Promising potential: Very high. GLP-1 receptor agonists are the fastest-growing drug class in endocrinology and metabolic medicine, with expanding indications (obesity, cardiovascular disease, chronic kidney disease, nonalcoholic steatohepatitis). Multiple compounds are approved by the FDA, EMA, and regulatory authorities worldwide.

Side-effect profile: Gastrointestinal adverse events (nausea, vomiting, diarrhea, constipation) are common and dose-limiting. Rare pancreatitis and medullary thyroid carcinoma signals are captured in prescribing labels. Cholelithiasis risk is elevated. Overall safety profile is well characterized through large clinical trials and postmarketing surveillance.

Overall validation: Very high. Multiple large randomized controlled trials, regulatory approval in multiple jurisdictions, extensive postmarketing experience, and dedicated cardiovascular and renal outcomes trials.

Comparison to Pancragen: GLP-1 receptor agonists and Pancragen operate through entirely different mechanisms (receptor-mediated incretin signaling versus proposed epigenetic transcription-factor modulation). The GLP-1 class has incomparably greater clinical validation, regulatory approval, effect size, and safety characterization. Pancragen's theoretical advantage is the proposed disease-modifying potential through restoration of beta cell identity rather than pharmacological augmentation of insulin secretion, but this advantage is unproven in clinical terms.

12.3 Exendin-4

Mechanism: A 39-amino-acid peptide originally isolated from the saliva of the Gila monster (*Heloderma suspectum*) that is a potent, long-acting GLP-1 receptor agonist. Exendin-4 is the parent molecule of the synthetic analog exenatide (Byetta, Bydureon). In addition to incretin effects, exendin-4 has demonstrated beta cell proliferative and anti-apoptotic effects in preclinical models, producing beta cell mass expansion in rodents [16].

Novelty: Low. The compound and mechanism have been characterized for over 30 years. The beta cell trophic effects are well known.

Effect size: Moderate to large for glucose lowering (HbA1c reduction 0.8 to 1.5 percent with exenatide). Beta cell mass expansion has been demonstrated in rodents but not confirmed in humans.

Promising potential: Moderate. Exenatide is approved and marketed but has been substantially superseded by longer-acting GLP-1 analogs (semaglutide, dulaglutide). Research interest in exendin-4 continues for beta cell biology and neuroendocrine applications.

Side-effect profile: Similar to the GLP-1 receptor agonist class: nausea, vomiting, injection site reactions. Rare pancreatitis. Well characterized through clinical use.

Overall validation: High. Approved drug with extensive clinical and preclinical literature.

Comparison to Pancragen: Exendin-4 shares the theoretical beta cell trophic activity with Pancragen but operates through receptor-mediated signaling rather than proposed epigenetic DNA binding. The beta cell proliferative effects of exendin-4 are better characterized than those of Pancragen and are supported by independent replication in multiple laboratories. Pancragen's proposed advantage (transcription-factor-level restoration of beta cell identity) is unproven relative to the well-characterized receptor-mediated trophic effects of exendin-4.

12.4 Harmine

Mechanism: A naturally occurring beta-carboline alkaloid that inhibits dual-specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A), producing robust human beta cell proliferation in vitro and in vivo. Harmine is the most potent and widely studied inducer of adult human beta cell proliferation identified to date, achieving proliferation rates of 1.5 to 3 percent of beta cells per day in human islet preparations [17].

Novelty: High. DYRK1A inhibition as a beta cell proliferation strategy was first reported in 2015 and represents a fundamentally new approach to beta cell mass expansion.

Effect size: Large in preclinical models. Harmine produces the highest rates of adult human beta cell proliferation reported for any compound. In combination with GLP-1 receptor agonists or TGF-beta pathway inhibitors, synergistic proliferation rates of 5 to 8 percent per day have been achieved in human islets [17].

Promising potential: Moderate. The compound faces substantial translational challenges: harmine is a promiscuous kinase inhibitor with central nervous system activity (monoamine oxidase inhibition, serotonergic and dopaminergic effects), and systemic administration produces psychoactive effects that limit clinical utility. Selective DYRK1A inhibitors and beta cell-targeted delivery strategies are in preclinical development.

Side-effect profile: Unfavorable for systemic use. Central nervous system effects (hallucinations, nausea, tremor) at doses that produce systemic DYRK1A inhibition. Cardiovascular effects. The compound is a controlled substance in some jurisdictions. The safety profile limits clinical translation despite the strong beta cell efficacy.

Overall validation: Moderate. Robust preclinical evidence from multiple independent laboratories. No clinical trials for diabetes indication. The compound serves as a proof of concept for DYRK1A-mediated beta cell proliferation.

Comparison to Pancragen: Harmine and Pancragen both aim to expand or restore functional beta cell mass, but through entirely different mechanisms (kinase inhibition driving cell cycle entry versus proposed epigenetic transcription-factor upregulation). Harmine has stronger and more independently replicated preclinical evidence for beta cell proliferation, but worse translational prospects due to its off-target pharmacology. Pancragen has better reported tolerability but weaker and less independently validated efficacy data.

12.5 Epithalon (Ala-Glu-Asp-Gly)

Mechanism: A synthetic tetrapeptide bioregulator developed by Khavinson as a pineal gland bioregulator (epiphysis-targeted). Epithalon acts through the same proposed epigenetic DNA-binding mechanism as Pancragen but targets different promoter sequences, upregulating telomerase (hTERT) expression, melatonin synthesis, and pineal gland function. Included in this comparison because it is the most extensively characterized Khavinson bioregulatory peptide and provides a benchmark for the validation level achievable within the Khavinson framework [10].

Novelty: Moderate within the Khavinson framework; the epigenetic peptide concept is the same as Pancragen. The telomerase activation claim is novel and distinctive.

Effect size: Reported effects include telomere elongation, melatonin level restoration, and lifespan extension in rodent models. Effect sizes are reported in Khavinson publications but have not been independently replicated.

Promising potential: Low. Not in pharmaceutical development outside the Khavinson network. Not approved by any Western regulatory authority. The telomerase activation claim has attracted interest in the longevity research community

but lacks independent validation.

Side-effect profile: No significant adverse effects reported. Safety data are limited and originate exclusively from the Khavinson network.

Overall validation: Moderate within the Khavinson framework (the most extensively published member of the class). Low by Western pharmaceutical standards (no independent replication, no regulatory-standard clinical trials).

Comparison to Pancragen: Epithalon and Pancragen share the same structural class, the same proposed mechanism (epigenetic DNA binding), and the same evidence-base limitations (Khavinson network exclusivity, absence of independent replication). Epithalon has a larger publication record and greater name recognition in the peptide research community. Pancragen has more directly disease-relevant clinical data (the type 2 diabetes study). The comparison illustrates the general state of validation for the Khavinson bioregulatory peptide class: plausible mechanism, consistent preclinical data within the originating network, and absent independent Western replication.

12.6 Comparator summary

The five comparators occupy distinct positions relative to Pancragen. **Suprefort** is the parent extract from which Pancragen was derived; Pancragen supersedes it as a defined, reproducible molecular entity. **GLP-1 receptor agonists** represent the gold standard for pharmacological management of type 2 diabetes with incomparably greater clinical validation; Pancragen does not compete on the same evidentiary plane but proposes a mechanistically distinct, potentially disease-modifying approach. **Exendin-4** shares the beta cell trophic concept with better-characterized receptor-mediated evidence. **Harmine** represents the strongest preclinical evidence for human beta cell proliferation but with prohibitive off-target pharmacology for clinical translation. **Epithalon** provides a within-class benchmark illustrating the general validation level of Khavinson bioregulatory peptides.

Pancragen occupies a unique niche in this comparator landscape: it is the only compound proposing to restore beta cell identity and function through direct epigenetic transcription-factor modulation at ultralow doses of a four-amino-acid peptide. The concept is scientifically intriguing and is supported by a coherent series of studies from cell culture through primate models to a small clinical study. The principal limitations are the absence of independent replication outside the Khavinson

network, the absence of formal pharmacokinetic characterization, the absence of regulatory-standard toxicology, and the small size and methodological limitations of the clinical evidence. Investigators considering Pancragen for research applications should weigh the mechanistic novelty against the evidentiary limitations and should design studies to provide independent validation of the key findings.

13. References

1. Khavinson VKh, Tendler SM, Kasyanenko NA, Tarnovskaya SI. Tetrapeptide KEDW interacts with DNA and regulates gene expression. *Am J Biomed Sci*. 2015;7(3):156-169.
2. Khavinson VKh, Linkova NS, Tarnovskaya SI. Short peptides regulate gene expression. *Bull Exp Biol Med*. 2016;162(2):288-292.
3. Khavinson VKh, Durnova AO, Polyakova VO, Tolibova GH, Linkova NS, Kvetnoy IM, Kvetnaia TV, Tarnovskaya SI. Effects of pancragen on the differentiation of pancreatic cells during their ageing. *Bull Exp Biol Med*. 2013;154(4):501-504.
4. Khavinson VKh, Gavrisheva NA, Malinin VV, Chefu SG, Trofimov EL. Effect of pancragen on blood glucose level, capillary permeability and adhesion in rats with experimental diabetes mellitus. *Bull Exp Biol Med*. 2007;144(4):559-562.
5. Khavinson VKh, Gapparov MM, Sharanova NE, Vasilyev AV, Ryzhak GA. Study of biological activity of Lys-Glu-Asp-Trp-NH₂ endogenous tetrapeptide. *Bull Exp Biol Med*. 2010;149(3):351-353.
6. Goncharova ND, Ivanova LG, Oganian TE, Vengerin AA, Khavinson VKh. Impact of tetrapeptide pancragen on endocrine function of the pancreas in old monkeys. *Adv Gerontol*. 2014;27(4):662-667.
7. Goncharova ND, Ivanova LG, Oganyan TE, Vengerin AA, Khavinson VKh. Correction of impaired glucose tolerance using tetrapeptide (Pancragen) in old female rhesus monkeys. *Adv Gerontol*. 2015;28(3):579-585.
8. Korkushko OV, Khavinson VKh, Shatilo VB, Antonyk-Sheglova IA, Bondarenko EV. Prospects of using pancragen for correction of metabolic disorders in elderly people. *Bull Exp Biol Med*. 2011;151(4):454-456.
9. Zakutskii AN, Chalisova NI, Ryzhak GA, Aniskina AI, Filippov SV, Zeziulin PN. The tissue-specific effect of synthetic peptides-biologic regulators in organotypic tissues culture in young and old rats. *Adv Gerontol*. 2006;19:93-96.
10. Khavinson VKh, Popovich IG. Peptide regulation of gene expression: a systematic review. *Molecules*. 2021;26(22):7053.

11. Khavinson VKh. Peptides and ageing. *Neuroendocrinol Lett.* 2002;23(Suppl 3):11-144.
12. Gao T, McKenna B, Li C, et al. Pdx1 maintains beta cell identity and function by repressing an alpha cell program. *Cell Metab.* 2014;19(2):259-271.
13. Maedler K, Schumann DM, Schulthess F, et al. Aging correlates with decreased beta-cell proliferative capacity and enhanced sensitivity to apoptosis: a potential role for Fas and pancreatic duodenal homeobox-1. *Diabetes.* 2006;55(9):2455-2462.
14. Adibi SA. The oligopeptide transporter (Pept-1) in human intestine: biology and function. *Gastroenterology.* 1997;113(1):332-340.
15. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2016;375(19):1834-1844.
16. Xu G, Stoffers DA, Habener JF, Bonner-Weir S. Exendin-4 stimulates both beta-cell replication and neogenesis, resulting in increased beta-cell mass and improved glucose tolerance in diabetic rats. *Diabetes.* 1999;48(12):2270-2276.
17. Wang P, Alvarez-Perez JC, Felsenfeld DP, et al. A high-throughput chemical screen reveals that harmine-mediated inhibition of DYRK1A increases human pancreatic beta cell replication. *Nat Med.* 2015;21(4):383-388.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly. Pancragen is not approved by the United States Food and Drug Administration, the European Medicines Agency, or any other major Western regulatory authority. The compound is marketed in Russia as a dietary supplement; investigators should consult their local regulatory authority before any research application. The preponderance of published evidence for Pancragen originates from a single research network (the Khavinson laboratory and collaborators at the Saint Petersburg Institute of Bioregulation and Gerontology); independent replication of key findings by investigators outside this network has not been published.