BPC-157 Thymosin Alpha 1 Thymosin Beta 4

## IMMUNE MODULATING PEPTIDES

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**Suncoast Hotel** 

**NOMA Summer 2019** 

#### **OBJECTIVES**

- Discuss the fundamentals of the Immune Modulating Peptides.
- Discuss the importance of the Cell signaling of Immune Modulating Peptides and its' downstream affects.
- Discuss clinical relevance's of BPC-157

### **BPC-157**



- Groups of organic molecules composed of:
  - Amino group (—NH<sub>2</sub>)
  - Acidic carboxyl group (—COOH),
  - Organic side chain (R group).

**Amino Acid Structure** 



- Essential Amino Acids:
  - Exogenous to the body
  - Taken in the form of food or other means.
     (Intravenous, transdermal or liquid).
  - Nine Essential A.A.
    - Histidine, Isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine



- Non-essential amino acids:
  - Internally generated
    - alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, proline, serine, and tyrosine



- Conditional A.A.
  - Non-essential except in time of stress
    - arginine, cysteine, glutamine, tyrosine, glycine, ornithine, proline, and serine

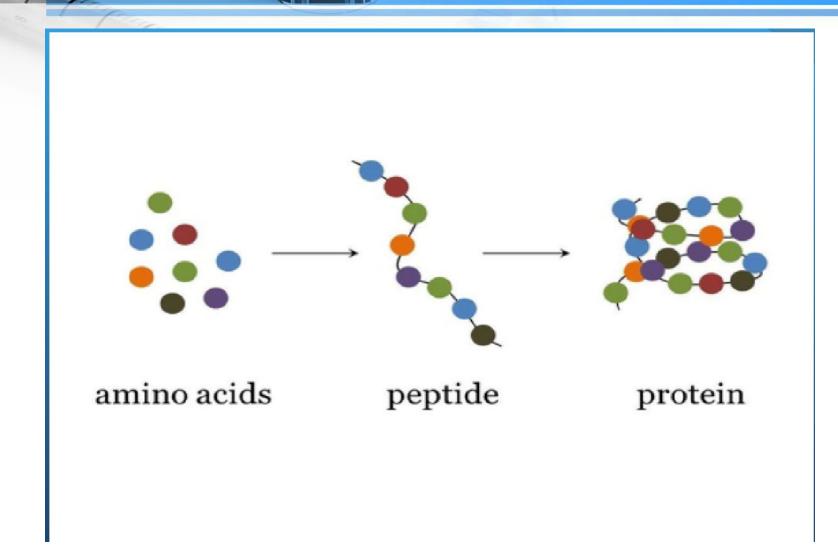


- Two or more amino acids linked by a peptide bond in a chain
- Protein chains are > 50 A.A. Combinations
- Enables
  - Growth
  - Repair
    - Gives cells and body, shape
  - Energy Source



- Structurally similar to proteins
- Contain less than 50 amino acid chains.
- "Oligopeptides," substances with less than twenty, or "polypeptides," consisting of 21-50 amino acids
- Sequence, shape, and type of amino acids involved determine a peptides' function.







- 7000 known Peptide Sequences
- 500 with sort of therapeutic value
- 60 approved (FDA) as medications.



- "A-G-E ing" = 4-letter word
- Built-in senescence=
  - Collagen breaks down.
  - Skin thins and wrinkles =
  - Damaged collagen layer
    - Message "We need more collagen."
    - Peptides produced, "messengers"
    - Regenerated tissues are incompletely repaired
      - Vicious cycle of breakdown and "disability" of the integumentary system.



- XYZ Collagen Skin Repair Cream
  - Peptides
  - The skin "misremembers" its' repair sequence
  - Accelerates the rate of new collagen restoration.



- 1<sup>st</sup> Peptide isolated: Insulin
- Peptides are Tissue Specific
- Hormones act globally on body
- Mitochondrial Messenger
  - Intimately involved in the inflammatory process



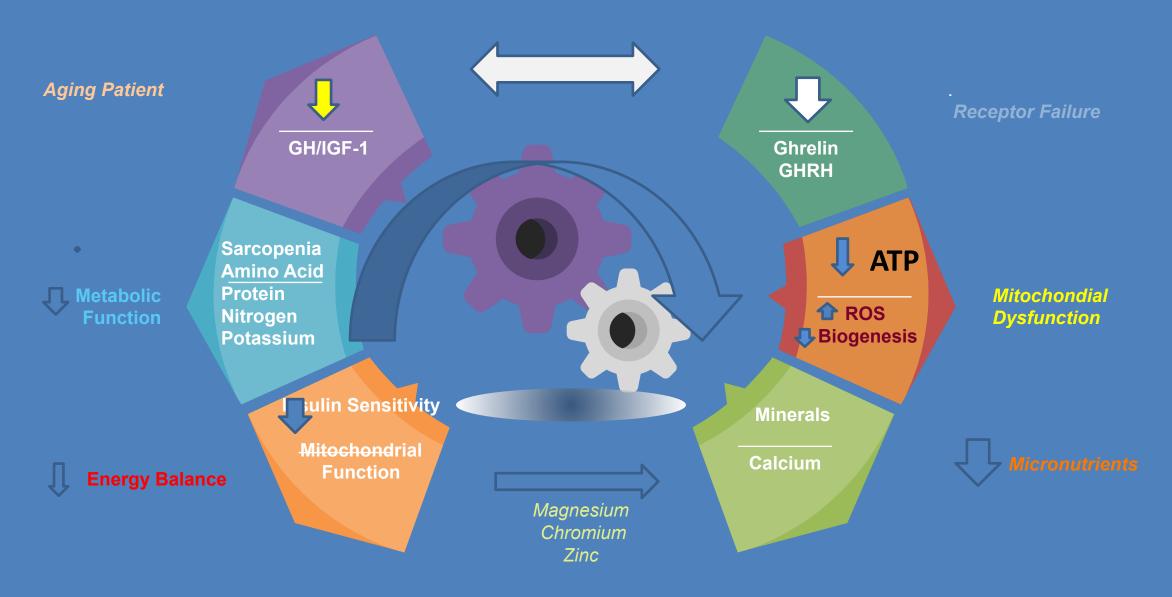
#### Aging

- Decrease GH,IGF-1
- Increase cellular Cortisol
- Sarcopenia (catabolic state)
- Decreased Insulin sensitivity-Mitochondrial dysfunction
- Decreased cognitive function and memory
- Decreased immune function
- Decreased Mitochondrial Biogenesis and efficiency with increased ROS
- Decreased steroid production ( mitochondria)

#### **Peptides**

- Immune enhancement
- Sleep
- Memory
- Depression/anxiety
- Improved cognition esp. post TBI
- Antimicrobial, anti-viral, anti-fungal, and antiparasitic agent
- Cellular rejuvenation and restoration
- Pain relief.

## Aging and GH/IGF-1





#### Growth Hormone Mimetics

- GHRH
  - Semorelean
  - CJC 1295 +/- DAC
- GHRP
  - GHRP 2
  - GHRP 6
  - Ipamorelin
  - Hexarelin

#### • Immune Modulating Peptides

- Thymosin Alpha 1 (TA1) (increases TH1)
- Thymosin Beta 4 (Tβ4) (increases TH1/decreases TH2))
- BPC-157 (decreases TH2/healing hormone) (oral, SQ, nasal, eye drops) "Homeostasis Peptide."
- Synergistic with pineal protein Epithalon

#### Rejuvenation/Pain

BPC-157, TB4, Epithalon, DSIP, GHRH/GHRP



- Brain peptides (memory, depression, anxiety, TBI, brain function, etc.)
  - Cerebrolysin
  - Semax
  - Selank
  - Synergistic with Epithalon, TB4, BPC-157, DSIP

#### Sleep peptides

- Epithalon "Homeostasis Peptide"
- Delta sleep-inducing peptide (DSIP)
- CJC/Ipamorelin (GHRH/GHRP) (other combo's)
- AOD

#### Antimicrobial peptides

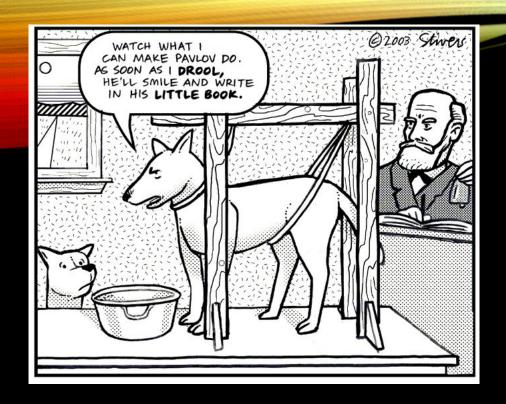
LL-37 (effective against Lyme cysts, viruses, fungal, parasites) (synergistic with TA1)

## Peptides Act As A Fine Tuning Mechanism

- Hormones
- Immune system
- Sleep
- Inflammatory cytokines
- Cell renewal
- Cancer cell destruction
- Libido

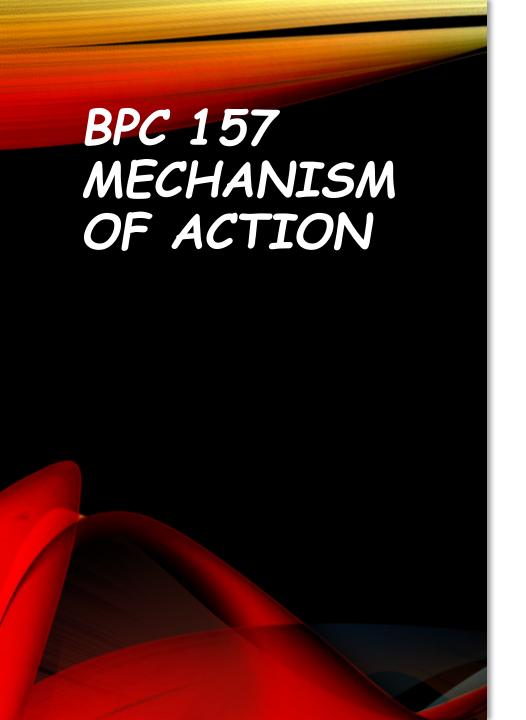
- Sexual arousal
- Weight loss
- Lean muscle gain
- Wound healing
- Brain function
- Urinary System
- Reproductive System.





## Back to Pavlov

- Isolated pure gastric juice from surgically prepared dogs.
- Calmed the gastrointestinal tract.
  - •Treated dyspepsia, gastritis, diarrhea, constipation, heartburn, poor appetite
    - •Stimulated red blood cell production.
    - Determined 12 years after his death to be intrinsic factor. Pavlov's "drug" relieved pernicious anemia.



...not just protect the brain from damage, but actually help replace and revitalize damaged cells.

> ...significantly accelerate bone healing

... protect and promote the health of the intestinal tract

> ... promote and accelerate wound repair

promote and restores healthy arteries and veins.

> ...protect the liver and promote its regenerative capacity

> > ...speed up the repair and regeneration of muscle and cartilage tissue

... reduce and reverse cardiac (=heart) damage.

#### BPC 157 MECHANISM OF ACTION

- BPC-157 promotes new vascular formation.
- Stimulates NO production.
- Stimulates angiogenic cytokines VEGF, FGF, and TGF-b
- Upregulates Anti-Inflammatory Gene Transcription Factor
- Sikiric P, et al. J Physiol Paris 87: 313–327, 1993.
- L. BRCIC1, I. BRCIC2, M. STARESINIC3, T. NOVINSCAK3, P. SIKIRIC3, S. SEIWERTH1, MODULATORY EFFECT OF GASTRIC PENTADECAPEPTIDE BPC 157 ON ANGIOGENESIS IN MUSCLE AND TENDON HEALING 1 Institute of Pathology, University of Zagreb Medical School, Zagreb, Croatia; 2. Clinical Department of Pathology and Cytology, University Hospital Center Zagreb, Zagreb, Croatia; 3. Department of Pharmacology, University of Zagreb Medical School, Zagreb, Croatia

### BPC 157 MECHANISM OF ACTION

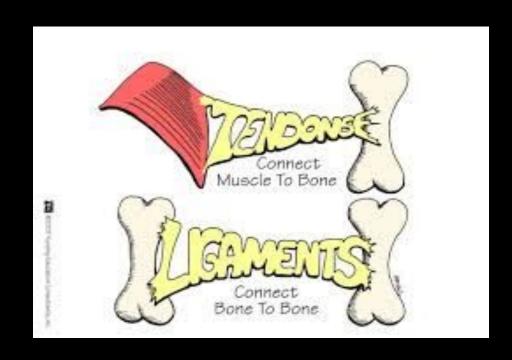
- Downregulates tumor necrosis factor (TNF)
- Influences corneal restoration
- Neuroregeneration, esp. from TBI
- Upregulates Growth Hormone receptors.

#### **BPC-157**



- **♦** Leukotriene B4
- Lipid mediators
  - Produced during inflammation.
- ❖ Thromboxane B
  - Vasoconstrictor/Hypertensive Agent
- Myeloperoxidase
  - Proatherogenic enzyme

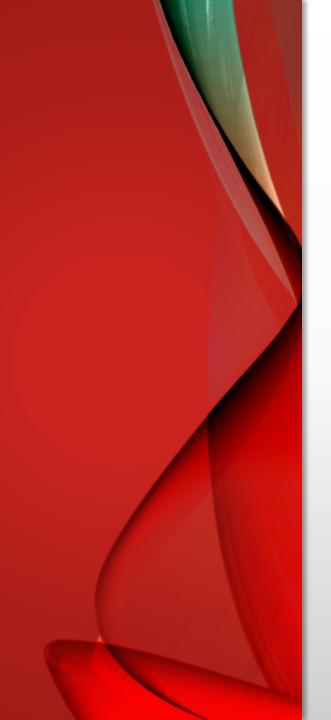
- Muscle Tissue Responds >Tendon
- Due to vascular affinity of BPC 157





# BPC 157 and Growth Factor Production

- Insulin derived growth factor
- Platelet-derived growth factor
- Transforming Growth Factor- Beta
- Basic fibroblast growth factor
- Vascular endothelial growth factor
- Growth Hormone (HGH)
  - HGH promotes cell regeneration and proliferation
  - HGH growth hormone increases collagen secretion.



# BPC 157 and Ligament Repair

- MCL Tear
  - Promotes microscopic regeneration
  - Functional recovery after injury
  - Stimulates granulation tissue collagen I production
  - Increases fibrin matrix repair mechanism.
  - The recovered ligamentous tissue is thicker and sturdier than before the injury.

#### BPC 157 AND CORTICOSTEROIDS

- Corticosteroids long term block nitric oxide collagen synthesis =
  - Atrophy of the treated joint, muscle, or tendon.

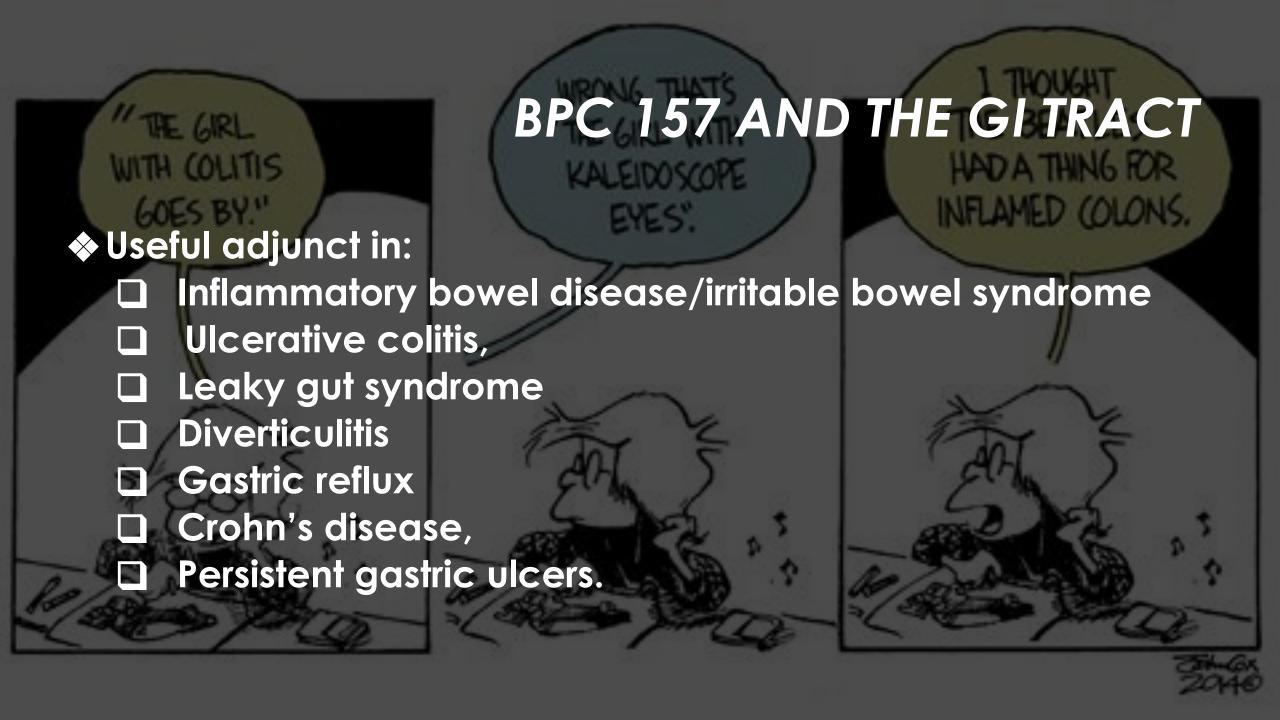
BPC Blocks Long Term Effects of Corticosteroid Injections

• BPC-157 protects endothelium and the formation of scar tissue



#### **BPC 157 AND THE GITRACT**

- Revives, repairs and rejuvenates the GI tract.
- Provides considerably more healing than:
  - # H2-blockers (ranifidine)
  - Proton pump inhibitors (omeprazole)
  - Gastric coating agents (sucralfate) (8)



#### **BPC 157 AND INFLAMMATION**

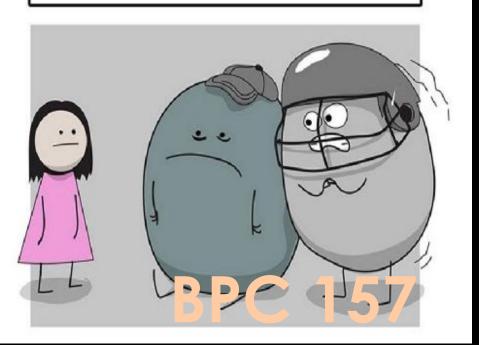
- Prevents and reverses:
  - Mitochondrial damage
  - Inflammatory aspects of rheumatoid arthritis
  - Inflammatory aspects of Lupus and Hashimoto's
  - Heals wounds in corneal epithelium.



#### BPC 157 AND ANXIETY/DEPRESSION

So I told her this:

Depression and anxiety are teammates and I'm the opposing team.



- Increases serotonin to a higher degree than SSRI
- Effective against both acute and chronic anxiety.

#### BPC 157 AND CARDIOVASCULAR S/S (14-17)

- Improves heart failure
- Stabilizes both high and low blood pressure
- Eliminates hyperkalemia (25)
- Prevents and reverses arrhythmias
  - A-Fib, A-V Block, Ventricular tach,
  - Premature atrial contractions
  - Premature ventricular contractions



# BPC 157 ADDS DIVERSITY TO YOUR RX. TOOL CHEST

- Reduces and reverses urinary stress incontinence
- Protects the liver in the face of alcohol-induced cirrhosis
- Cytoprotective from NSAID administration, mold, C. difficile, and neurotoxins. (18-21)
- Prevents hepatic encephalopathy
- Interacts with dopamine, serotonin, opioid, and GABA neurotransmitters
- Prevents glutathione depletion. (22)
- Mitigates neuronal damage, improves early outcomes, and delays mortality in 1<sup>st</sup> 24 hours post TBI. (23-24)

# BPC 157 ADDS DIVERSITY TO YOUR RX. TOOL CHEST

- Attenuates: (25)
  - Behavioral agitation
  - Muscle twitches
  - Restless leg syndrome, leg contractures,
  - Edema
  - Atrophic muscles.
- Enhances: (26-28)
  - GH (increases GH receptors)
  - Outperforms acyclovir in the treatment of HSV infection,
  - Normalizes esophageal and pyloric sphincter control.

# BPC 157 ADDS DIVERSITY TO YOUR RX. TOOL CHEST

- Multiple Sclerosis (29)
  - Decreased nerve damage in the corpus callosum, the laterodorsal thalamus, and anterior horn motor neurons.

• Wound healing in alkali chemical burns (Topical). (30)

Corneal abrasions responded 2 pg/ml, 2 ng/ml, 2ug/ml strength. (31)

• 2 drops were administered drops every 8 hours for 40 hours.

### SAFETY OF BPC 157

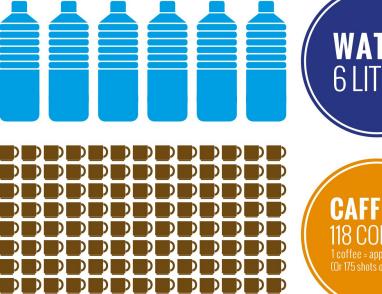
- No lethal dose (LD1) to kill 1% of the population
  - could be found. (32)
- By contrast, the lethal dose 50 (i.e., the dose need population weighing 75 kg is: (33)
  - 6 liters for water
  - 175 shots of espresso
  - 13 shots of 40% proof alcohol.

#### LETHAL DOSES OF COMMON CHEMICALS



LD<sub>50</sub> stands for 'median lethal dose', and is defined as the amount of a substance required to kill 50% of a test population of animals, expressed in mg per kg of body weight. Human LD<sub>EO</sub> values are calculated from these tests. For ethical reasons, tests on animals to determine LD<sub>50</sub> are being phased out in favour of other methods.

The figures provided below are median lethal doses, and are rough averages for a body weight of 75kg, when the amount specified is taken all at once. Actual figures will vary depending on physical and medical condition.













## SUMMARY OF POTENTIAL THERAPEUTIC USES (34)

- Lyme disease/HIV (especially in conjunction with TA1)
- Chronic viral or intracellular infections
- CFS/Fibromyalgia
- Autoimmune disease (asthma, lupus, etc..)
- Inflammatory conditions (markers: CRP, C4a,

#### **ESR**

- CVD
- Post-surgical
- Diabetes
- Aging
- Allergies/MCAS
- Chemical sensitivity
- GI ulcers/inflammation
- Inflammatory bowel disease
- Leaky Gut
- H-pylori and GERD
- Periodontitis
- Prevent/treat heart arrhythmias

- Mold and toxin exposure
- Neurodegenerative disease
- Muscle/tendon/Bone repair
- Pain Syndromes
- Eye inflammation and dry eye (with TB4 and stem cell eye drops)
- Mitochondrial dysfunction
- Depression anxiety
- Heart disease/dysfunction
- Given with stem cells (with TB4)
- Urinary incontinence
- Hyper and hypercoagulability
- HTN and hypotension
- Adjunct to growth hormone replacement (increases GH receptors)
- Viral infections
- Hypothyroidism/thyroid resistance
- Boosts mitochondrial function

**TBI** 

### BPC 157 DOSING

- Dosing:
  - (Packaged in 2000 mcg/ml 5 ml vials.)
  - Oral Capsules 500 mcg

Orally: 500 mcg troche/capsule for GERD.

 SQ: 800-1000 mcg SQ2x/d x 4-7 days for acute injury.

 Joint injection: 1-2 ml. Mix with 1-5 cc of Platelet Rich Plasma.

• Or

0.15 ml sq daily

an

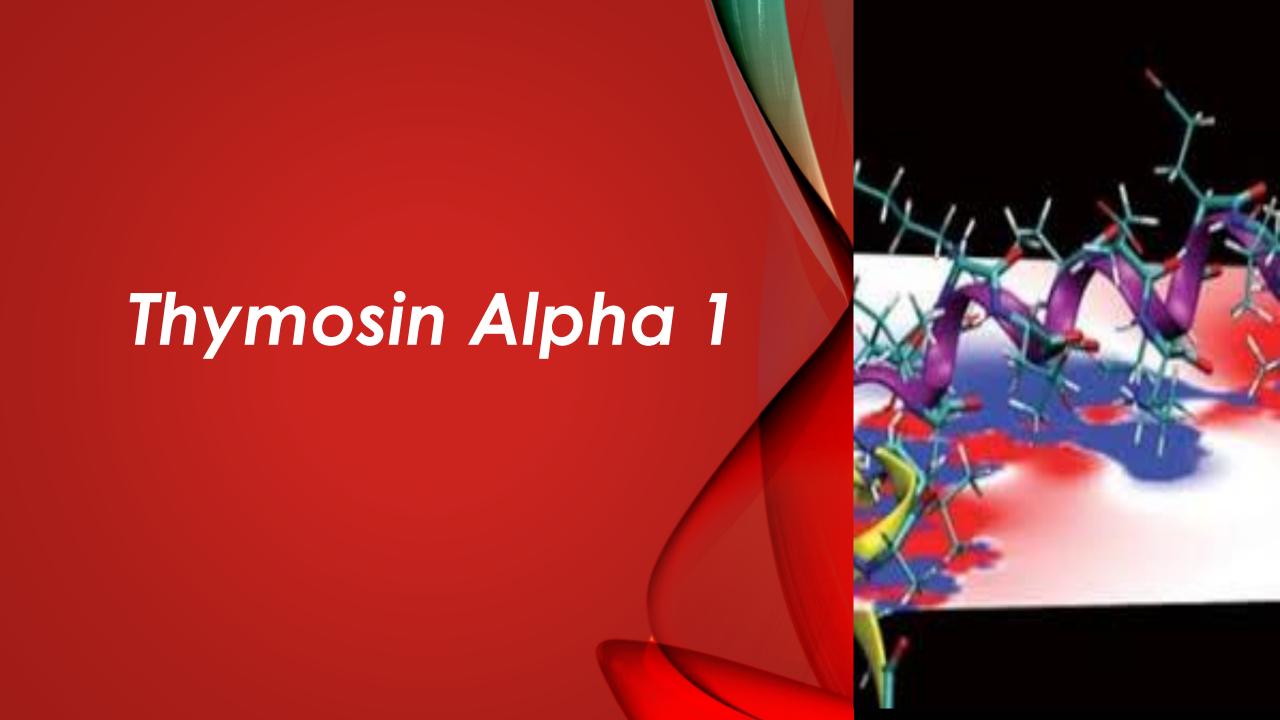
• IV: 2.5 ml (3 mg) with 5 ccs normal saline over 24 minutes for pain.

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## Thymosin Alpha 1-Indications (5)

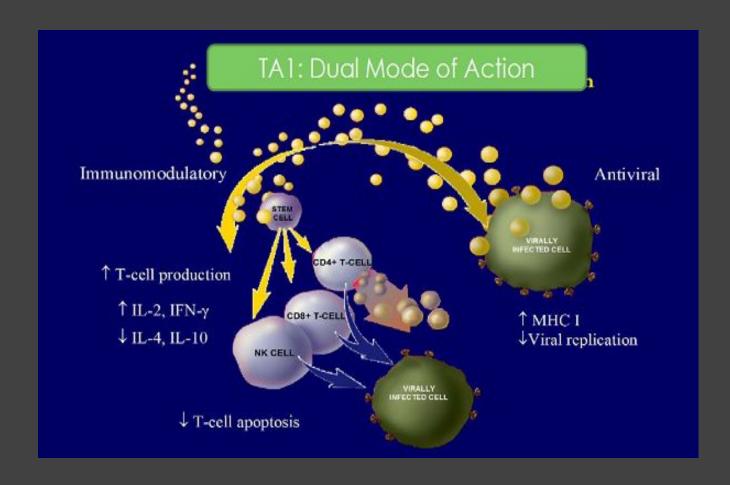
- Hepatitis B & C
- HIV/AIDS
- Cancer non-small cell lung (NSCLC), hepatocellular, malignant melanoma
- Chemotherapy adjunct-Reduces hematologic side effects with:
  - Cyclophosphamide
  - 5-fluorouracil (5FU)
  - Dacarbazine
  - Isocyanide
- Chronic inflammatory conditions including autoimmunity
- Cystic fibrosis
- Lyme disease

## Thymosin Alpha 1-Indications (5)

### Anything Requiring an Immune Response

- Steroid-induced apoptosis of thymocytes
- Depressed response to vaccinations; adjunct to the flu vaccine
- Geriatric immune support
- DiGeorge's syndrome
- Sepsis
- Influenza preventive

## Thymosin Alpha 1-Mechanism of Action



Improves anti-inflammatory cytokines IL-1 beta, IFN- γ, IL-2, IL-3, IL-6, IL-10. (8-9)

CD3+, CD4+ and CD8+, antioxidant activity by specifically improving intracellular glutathione.

## Thymosin Alpha 1-Clinical Pearls

Prolonged mean lifespan by 28% and exhibited a 2.8-fold reduction in all cancers. (18)

Nonresectable non-small cell lung cancer demonstrated a statistically significant improvement in relapse-free survival (P=0.04) when *TA1* was administered for up to 1 year following radiation therapy.

Overall survival (P=0.009) correlated with T cell restoration to pretreatment levels. (19)

## Thymosin Alpha 1 In Clinical Practice (20)

- Women have significantly lower intrinsic TA1 than men (P < 0.0001)</p>
- Autoimmune patients are significantly lower in TA1 levels than healthy controls. (P < 0.0001)</p>
- Patients on disease-modifying, anti-rheumatic drugs (DMARD) exhibit significantly higher TA1 than autoimmune patients not on DMARDs. The DMARDs crowd remains lower than healthy controls, however.
- TA1 levels are significantly lower in patients with severe infections and cancer.

## Thymosin Alpha 1-Side Effects (21)

- o Redness and pain at the injection site.
  - o Generalized erythema, transient muscle atrophy, polyarthralgia, and rash.
  - o A transient increase in ALT, up to twice baseline.
  - Current recommendations include continuing therapy unless frank signs of liver failure occur.

## Thymosin Alpha 1-Brand Name Drug

Thymalfasin Brand Name- Zadaxin)

Proprietary thymosin alpha 1 product

Developed by the Shanghai-based SciClone Pharmaceuticals Holding Company.

Approved in 30 countries for hepatitis B and C and as a cancer chemotherapy adjunct. (22)

Indicated for: (23-24)

Mono or combination therapy with interferon for the treatment of chronic hepatitis B and C. Non-small cell lung cancer (NSCLC), hepatocellular carcinoma, AIDS, and malignant melanoma.

#### Dose:

- 1.6 mg, injected SubQ, 2 times weekly for 6-12 months
- Patients weighing < 40 kg, dosage adjusted to 40 mcg/kg, 2 times weekly.</li>

## Thymosin Alpha 1-Dose

### Dosage

1.5 mg subcutaneous (SQ) every third day

#### RX:

- Viral Infection-2 weeks
- HIV/Cancer/Hepatitis/Complicated immune suppression/over-activation-3 mo.

Has a 2-hour Half-Life

## Thymosin Alpha 1 and COVID 19

Genes associated with cytokine signaling and production were upregulated in blood cells from patients with COVID-19

Treatment with  $T\alpha 1$ -mitigated cytokine expression inhibited lymphocyte activation in a CD8+ T-cell subset specifically.

Overexpression of IL-6, TNF $\alpha$ , LTA, IL-1 $\beta$ , and IL-10 and chemokines CCL2 (also known as MCP1) and CXCL6

TA 1down regulates II-6, TNF a, IL-1 B and upregulates IL-10

Claudia Matteucci, Antonella Minutolo, Emanuela Balestrieri, Vita Petrone, Marialaura Fanelli, Vincenzo Malagnino, Marco Ianetta, Alessandro Giovinazzo, Filippo Barreca, Silvia Di Cesare, Patrizia De Marco, Martino Tony Miele, Nicola Toschi, Antonio Mastino, Paola Sinibaldi Vallebona, Sergio Bernardini, Paola Rogliani, Loredana Sarmati, Massimo Andreoni, Sandro Grelli, Enrico Garaci, Thymosin Alpha 1 Mitigates Cytokine Storm in Blood Cells From Coronavirus Disease 2019 Patients, Open Forum Infectious Diseases, Volume 8, Issue 1, January 2021, ofaa588, <a href="https://doi.org/10.1093/ofid/ofaa588">https://doi.org/10.1093/ofid/ofaa588</a>

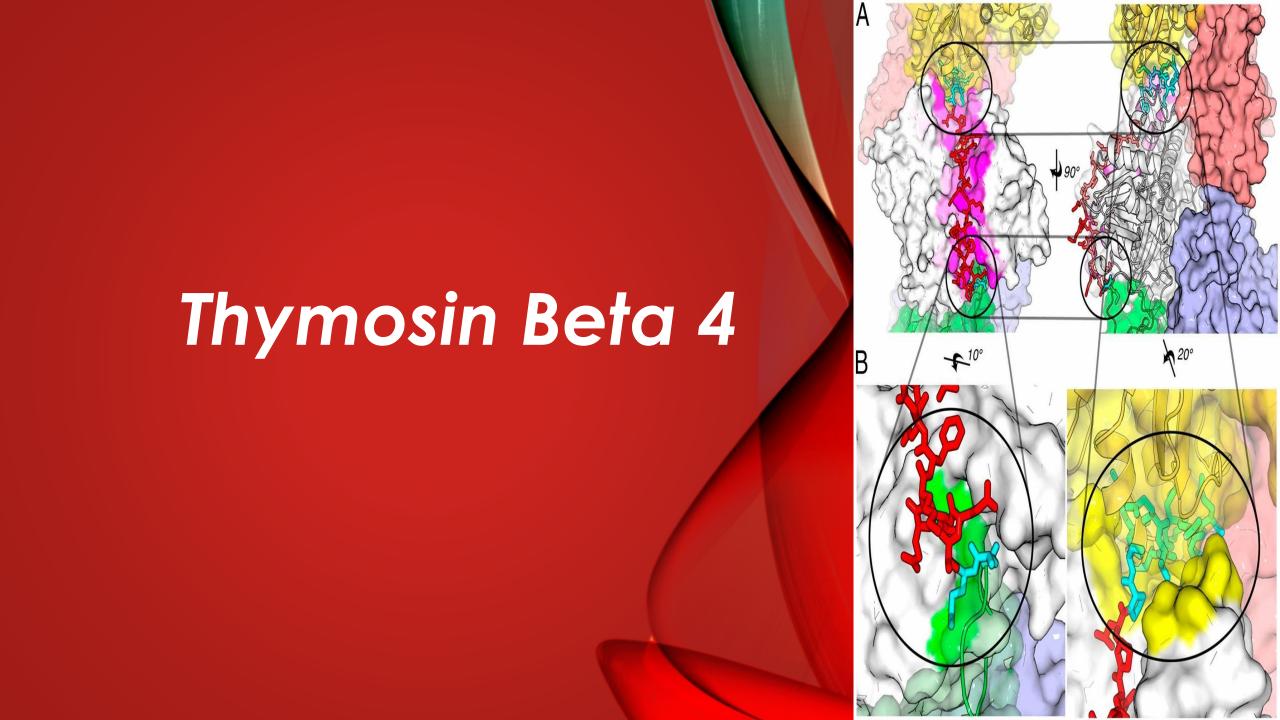
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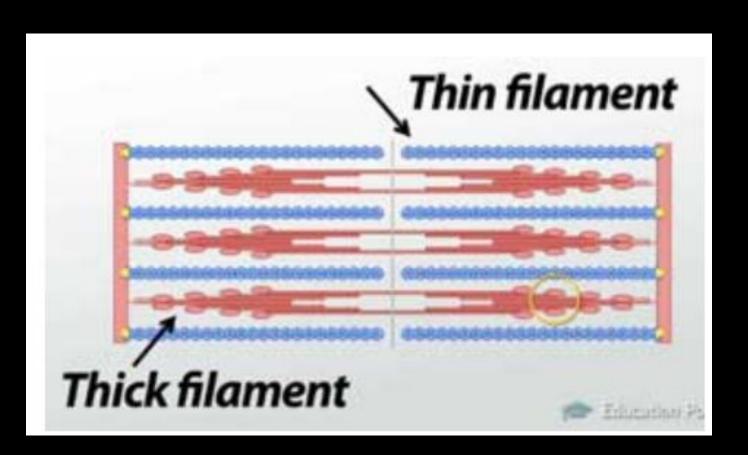
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### **MUSCLE FUNCTIONS**

 Muscles contract and relax by the sliding of one protein, myosin, over the other protein, actin, in a series of repetitive events. (1)

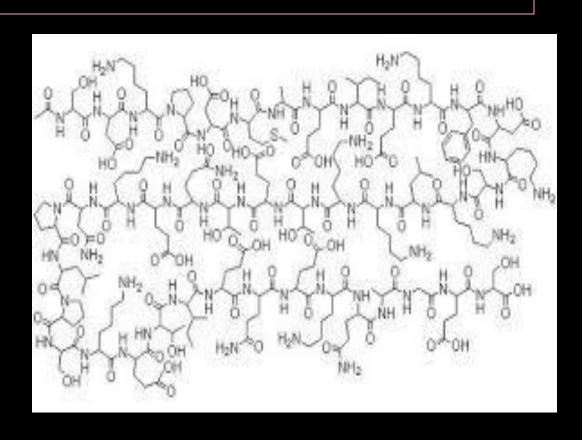
 Myosin is a thick motor protein, and actin is the thinner, scaffolding filament.



#### • 43 amino acid peptide

- Fund in almost every cell in the body,
- Upregulates actin, responsible for <u>muscle</u> <u>contraction</u>
- Stimulates the formation of healing cells
- Improves cell migration to a site of injury. (3)
- Anti-inflammatory, antiviral
- Cardio and neuroprotective.

## THYMOSIN BETA 4



a)

## Thymosin Beta 4 and Infectious Diseases

#### Acute

- Influenza
- URI
- Ebola
- Zika viruses.

#### Chronic

- HIV
- Lyme disease
- Malaria
- Herxheimer reactions (4)
- Combine w Cipro for Improved response to

  Pseudomonas aeruginosa in the eye (6)

# Thymosin Beta 4 and Chronic Inflammatory Diseases (5)

- MI
- Pre and post-op surgical preparation and recovery
- Remyelinating nerve tissue damaged: Alzheimer's
  - MS
  - Peripheral neuropathy.

- Hepatoprotective in alcohol and LPS liver injury
- Prevents ethanol and LPS mediated increases liver enzymes
- Prevents jumps in LPS and alcohol-induced oxidative stress.
- Decreases reactive oxygen species and lipid peroxidation
- Increases antioxidants
  - Glutathione

Manganese-dependent superoxide dismutase.

• Prevents excess proinflammatory cytokine formation and liver fibrosis. (7)

Thymosin Beta 4 and Chronic Inflammatory Diseases (5)

Wound repair.

**Anti-inflammatory** 

angiogenesis

Increases collagen deposition,

Cytoprotective. (8)

**Angiogenesis** 

**Antifibrosis** 

Reduces infarct volume

**Preserves cardiac function** 

Improves cardiac wound repair.

a)

## Thymosin Beta 4 in Clinical Practice (5)

- Soft Tissue Repair—tendons, ligaments, muscle, sport, and athletic injuries.
- ✓ Pressure or venous stasis ulcers.
- Conditions requiring immune response modulation
- ✓ Brain issues if autoimmunity suspected
- Ischemic stroke
- Spinal cord injuries
- ✓ TBI / concussion/MS (in conjunction with BPC-157)
- Dry eye disorders

a)

## Thymosin Beta 4 in Clinical Practice (5)

- Phase II clinical trials –RegeneRx
- Corneal injuries
- Phase 3 US trial for Epidermolysis bullosa
- Lung inflammation –pulmonary fibrosis
- May improve hair growth
- Non-Alcoholic Fatty Liver
  - Inhibits oxidative stress
  - Decreases proinflammatory cytokines
  - Decreases hepatic fibrosis
- Cardioprotective
- Reduces endotoxemia-use in sepsis
- Reduces mortality

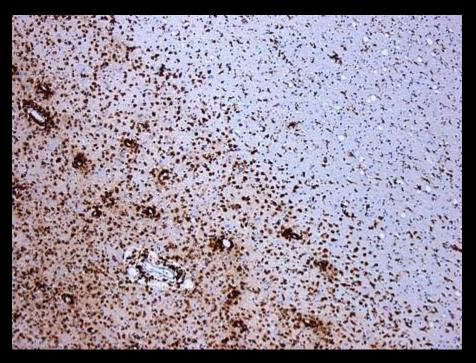
## Thymosin Beta 4 and Multiple Sclerosis

- Demyelinating disease
- Affects brain and spinal cord
- T cells penetrate BBB
- Initiate myelin attack
- Autoreactive lymphocytes
- Treatment options limited

- M.S. presents w infectious etiology. (11)
- Epstein-Barr virus (EBV) explains the key features of MS epidemiology. (12)
- 10-20 fold increase in incidence of M.S w EBV infections, (13)

## Thymosin Beta 4 and Multiple Sclerosis

- MS + TB 4 =
  - Improved functional outcomes.
  - Neuroprotective and anti-inflammatory
  - Neuroregenerative
    - Neurons, oligodendrocytes, microglia.
    - Restores myelin,
    - Synaptogenesis,
    - Enables axon growth.



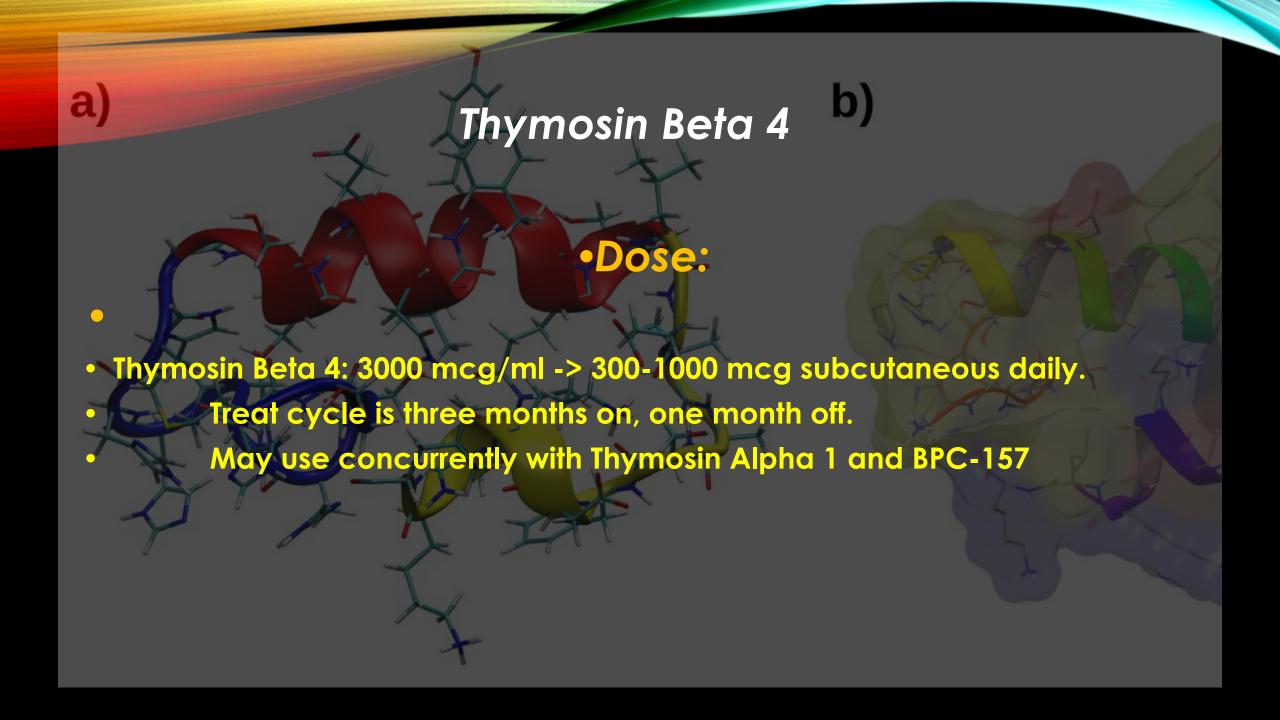
Demyelination by MS. The CD68 colored tissue shows several macrophages in the area of the lesion Thymosin Beta 4, Thymosin Alpha 1 and Multiple Sclerosis **TB 4 TB** 1

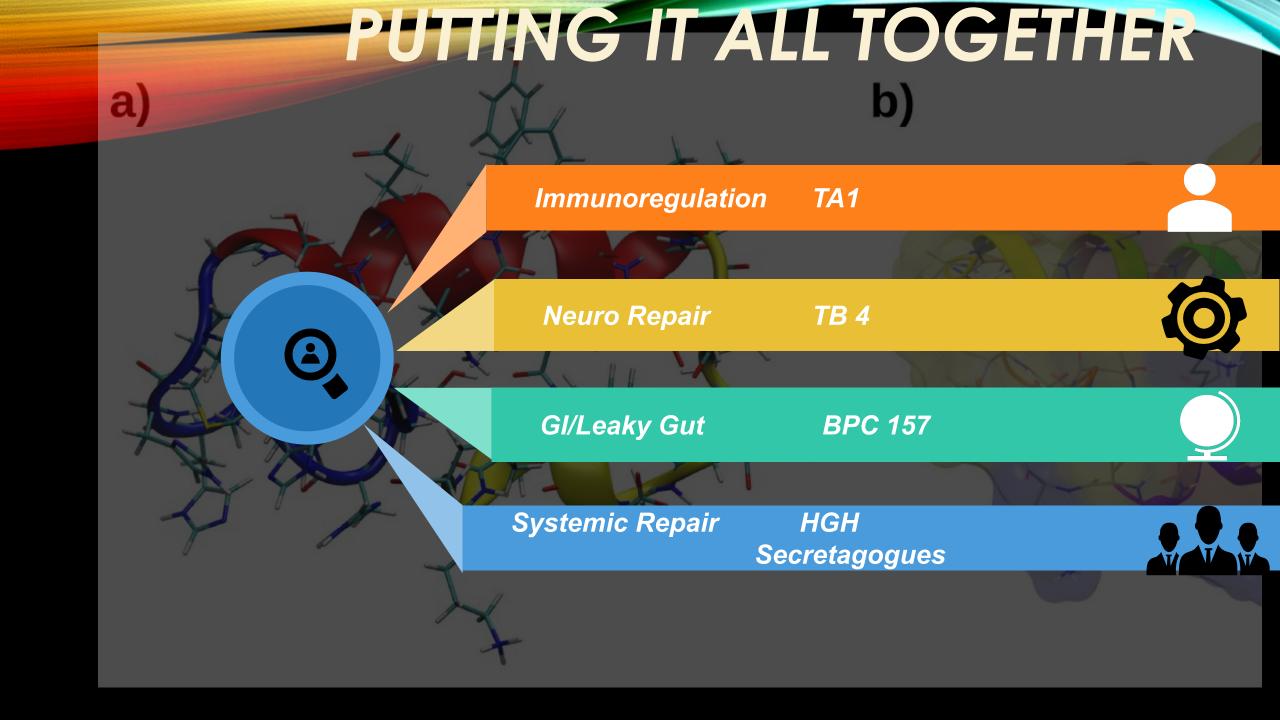
- Targets multiple cells
- **Neurorestorative:**
- Reduces Axonal Damage,

**Apoptosis** 

- Remyelinating
  - **Rewrapping of Axons**
- Neuroprotective
- **Anti-inflammatory**

- **Pleiotropic**
- Adaptogenic
- **Induces Regulatory B Cells**
- **Reduces Proinflammatory B** Cells
- **Anti-Inflammatory**
- **Anti-viral**





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				Inflammat	Libid		Weight	Cogniti		Slee		
	Class	Pain	ity	ion	0	ging	Loss	ve	ant	р	Dose	Conditions
Thymosin Alpha 1	TH 1 Stimulation	+	+++	++		++		+	++		50-300 mcg/d	Immune boost; CA, Infectons
Thymosin Beta 4	TH1/TH2 Balance	++	+++	+++		++		++	++	+	50-300 mcg/d	Immune moduclatio n, CA, Neurorejuve nation, muscle pain
BPC 157	Anti inflammator y	+++	+++	+++		+++	+	+	+++	+	Oral 500 mg	Wound healing, orthopedic repair, GI Healing, rejuvenatio n
	Pineal Peptide										50-150mg/	Anti-biofilm, infections, Lyme, anti-bacteri al, antibiotic, antiviral,

			36						Pepti	ide	Sun	nmary
	Class	Pain	Immunity	Inflammation	d	Anti- Agin g	Weight		Antioxidan			Conditions
PT-141	MSH Analog				++ +	-	+				1-2 mg 2x/d	Libido, Weight Loss, Tanning
GHRH/GHRP	HGH Mimic		+	+		+	+	+		++	160-400 mg @ hs	Healing, Body Fat, Rejuvenatio n
Semax	Nootropi c	+	+	++	+	+++		+++	++	+	100-300 mg/d	Cognitive Dysfunction, Memory,
	Nootropi c		+	+		+		++	+	++		Dementia, Stroke, TBI
CJC/Ipamor elin	GHRP/GH Rh		+	+		++	+	+		++	150-300 mg/d	GH Stimulation

