IMMUNE MODULATING PEPTIDES

William Clearfield D.O.
Suncoast Hotel
NOMA Summer 2019

BPC-157
Thymosin Alpha 1
Thymosin Beta 4
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
• 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.
BPC 157
MECHANISM OF ACTION

...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


• L. BRCIC1, I. BRCIC2, M. STARESINIC3, T. NOVINSCAK3, P. SIKIRIC3, S. SEIWERTH1. MODULATORY EFFECT OF GASTRIC PENTADECAPTIDE BPC 157 ON ANGOGENESIS IN MUSCLE AND TENDON HEALING 1Institute 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.
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.
• **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.
• 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 GI TRACT

- Revives, repairs and rejuvenates the GI tract.
- Provides considerably more healing than:
  - H2-blockers (ranitidine)
  - Proton pump inhibitors (omeprazole)
  - Gastric coating agents (sucralfate) (8)
BPC 157 AND THE GI TRACT

- Useful adjunct in:
  - Inflammatory bowel disease/irritable bowel syndrome
  - Ulcerative colitis,
  - Leaky gut syndrome
  - Diverticulitis
  - Gastric reflux
  - Crohn’s disease,
  - Persistent gastric ulcers.
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**

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

“For years your teachers kept telling you to settle down and sit still. You can stop now.”
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 1st 24 hours *post TBI*. (23-24)
BPC 157 ADDS DIVERSITY TO YOUR RX. TOOL CHEST

- **Attenuates:**
  - Behavioral agitation
  - Muscle twitches
  - Restless leg syndrome, leg contractures,
  - Edema
  - Atrophic muscles.

- **Enhances:**
  - GH (increases GH receptors)
  - Outperforms acyclovir in the treatment of HSV infection,
  - Normalizes esophageal and pyloric sphincter control.
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 needed to kill 50% of a given population weighing 75 kg is: (33)
  • 6 liters for water
  • 175 shots of espresso
  • 13 shots of 40% proof alcohol.
<table>
<thead>
<tr>
<th>Lyme disease/HIV (especially in conjunction with TA1)</th>
<th>Mold and toxin exposure</th>
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<tbody>
<tr>
<td>Chronic viral or intracellular infections</td>
<td>Neurodegenerative disease</td>
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<tr>
<td>CFS/Fibromyalgia</td>
<td>Muscle/tendon/Bone repair</td>
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<tr>
<td>Autoimmune disease (asthma, lupus, etc..)</td>
<td>Pain Syndromes</td>
</tr>
<tr>
<td>Inflammatory conditions (markers: CRP, C4a, ESR)</td>
<td>Eye inflammation and dry eye (with TB4 and stem cell eye drops)</td>
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<tr>
<td>CVD</td>
<td>Mitochondrial dysfunction</td>
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<tr>
<td>Post-surgical</td>
<td>Depression anxiety</td>
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<tr>
<td>Diabetes</td>
<td>Heart disease/dysfunction</td>
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<tr>
<td>Aging</td>
<td>Given with stem cells (with TB4)</td>
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<tr>
<td>Allergies/MCAS</td>
<td>Urinary incontinence</td>
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<tr>
<td>Chemical sensitivity</td>
<td>Hyper and hypercoagulability</td>
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<tr>
<td>GI ulcers/inflammation</td>
<td>HTN and hypotension</td>
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<tr>
<td>Inflammatory bowel disease</td>
<td>Adjunct to growth hormone replacement (increases GH receptors)</td>
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<tr>
<td>Leaky Gut</td>
<td>Viral infections</td>
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<tr>
<td>H-pylori and GERD</td>
<td>Hypothyroidism/thyroid resistance</td>
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<tr>
<td>Periodontitis</td>
<td>Boosts mitochondrial function</td>
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<tr>
<td>Prevent/treat heart arrhythmias</td>
<td>TBI</td>
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</tbody>
</table>
• 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 an acute injury.

  • Or
  
  0.15 ml sq daily

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

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2. 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 1Institute 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


30. KLICEK R ET AL. JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2013, 64, 5, 597-612


34. Huang T., et al. DRUG DESIGN, DEVELOPMENT, AND THERAPY 2015:9 2485–2499

35. Holtorf, K. A4M: International Peptide Society Certification Course. Las Vegas Nevada, December 12-16, 2018

Thymosin Alpha 1
Thymosin Alpha 1 - Indications

- 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

• 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
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.
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)
Women have significantly lower intrinsic TA1 than men (P < 0.0001)

Autoimmune patients are significantly lower in TA1 levels than healthy controls. (P < 0.0001)

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.
Redness and pain at the injection site.

Generalized erythema, transient muscle atrophy, polyarthralgia, and rash.

A transient increase in ALT, up to twice baseline.

Current recommendations include continuing therapy unless frank signs of liver failure occur.
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)


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.
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
REFERENCES


20. International Peptide Society, Thymosin Alpha 1 Monograph, 2018, Cincinnati, OH, 2018; 8


Thymosin Beta 4
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 muscle contraction

• Stimulates the formation of healing cells
• Improves cell migration to a site of injury. (3)

• Anti-inflammatory, antiviral

• Cardio and neuroprotective.
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)
a) Thymosin Beta 4 and Chronic Inflammatory Diseases

- 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

Wound repair.
Anti-inflammatory
angiogenesis
Increases collagen deposition,
Cytoprotective. (8)
Angiogenesis
Antifibrosis
Reduces infarct volume
Preserves cardiac function
Improves cardiac wound repair.
Thymosin Beta 4 in Clinical Practice

- 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
• 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
• 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

<table>
<thead>
<tr>
<th><strong>TB 4</strong></th>
<th><strong>TB 1</strong></th>
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<tbody>
<tr>
<td>- Targets multiple cells</td>
<td>- Pleiotropic</td>
</tr>
<tr>
<td>- Neurorestorative:</td>
<td>- Adaptogenic</td>
</tr>
<tr>
<td>- Reduces Axonal Damage, Apoptosis</td>
<td>- Induces Regulatory B Cells</td>
</tr>
<tr>
<td>- Remyelinating</td>
<td>- Reduces Proinflammatory B Cells</td>
</tr>
<tr>
<td>- Rewrapping of Axons</td>
<td>- Anti-Inflammatory</td>
</tr>
<tr>
<td>- Neuroprotective</td>
<td>- Anti-viral</td>
</tr>
<tr>
<td>- Anti-inflammatory</td>
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</tbody>
</table>
Dose:

- Thymosin Beta 4: 3000 mcg/ml -> 300-1000 mcg subcutaneous daily.
- Treat cycle is three months on, one month off.
- May use concurrently with Thymosin Alpha 1 and BPC-157


4. Carion TW, Kracht DJ, Strand E, et al. Thymosin beta-4 and Ciprofloxacin Adjunctive Therapy Improves Pseudomonas Aeruginosa Induced Keratitis. 5th International Symposium in health and disease; Thymosins, Nov 15-17, 2017


6. Carion TW, Kracht DJ, Strand E, et al. Thymosin beta-4 and Ciprofloxacin Adjunctive Therapy Improves Pseudomonas Aeruginosa Induced Keratitis. 5th International Symposium in health and Disease; Thymosins, Nov 15-17, 2017


12. IBID

13. IBID


15. Severa, M., et. Al; Multiple Sclerosis and Related Disorders 27 (2019) 52-60
To Learn More Come to the American Osteopathic Society of Rheumatic Diseases OMED 2019, October 25-28, 2019

And

Congress of Medical Excellence 2.0 Reno, NV February 28, 29, March 1, 2020

Thank You