

# Peptides for Neurodegenerative Disorders

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# Background

- Peptides on “fringes” of medicine until recently

- Past Problems

- High costs
- Limited availability
- Short half-lives
- Lack of oral bioavailability
- Side effects
- Poor patient compliance with injections
- Regulatory environment
- Sub-quality products readily available on internet



Bruno BJ, Miller GD, Lim CS. Basics and recent advances in peptide and protein drug delivery. *Ther Deliv.* 2013;4(!1):1443-1467.

# Background

- What Changed?
  - Genomics, Metabolomics, Proteomics
  - Recombinant technology and genetic engineering
  - Pharma Driven
- Improved bioavailability
- Decreased side effects
- Improved efficacy and safety

Bruno BJ, Miller GD, Lim CS. Basics and recent advances in peptide and protein drug delivery. *Ther Deliv.* 2013;4(!1):1443-1467.

# Peptides for Neurological Disorders

- Growth hormone supportive
- Neuroprotective/Neuroregenerative
- Decreases microglial inflammation
- GUT-BRAIN axis support
- Immune supportive

# GH & Brain

- GH receptor and GH itself are expressed widely in the brain
- Dysfunction of GH / IGF-1 axis common in neurodegenerative diseases
- GH has been reported to alter:
  - Neurogenesis
  - Myelin synthesis
  - Dendritic branching
  - Neural stem cells which are activated by GH
- GH occurs in the hippocampus in response to a memory task
- Down stream IGF-1, IGF-2

Bianchi VE, et al. Neurotrophic and neuroregenerative effects of GH/IGF-1. *Int J Mol Sci.* 2017;18(11):2441.

Gasperi M, et al. Growth hormone/insulin-like growth factor I axis in neurodegenerative diseases. *J Endocrin Invest.* 2010;33:587-91.

# GH Brain

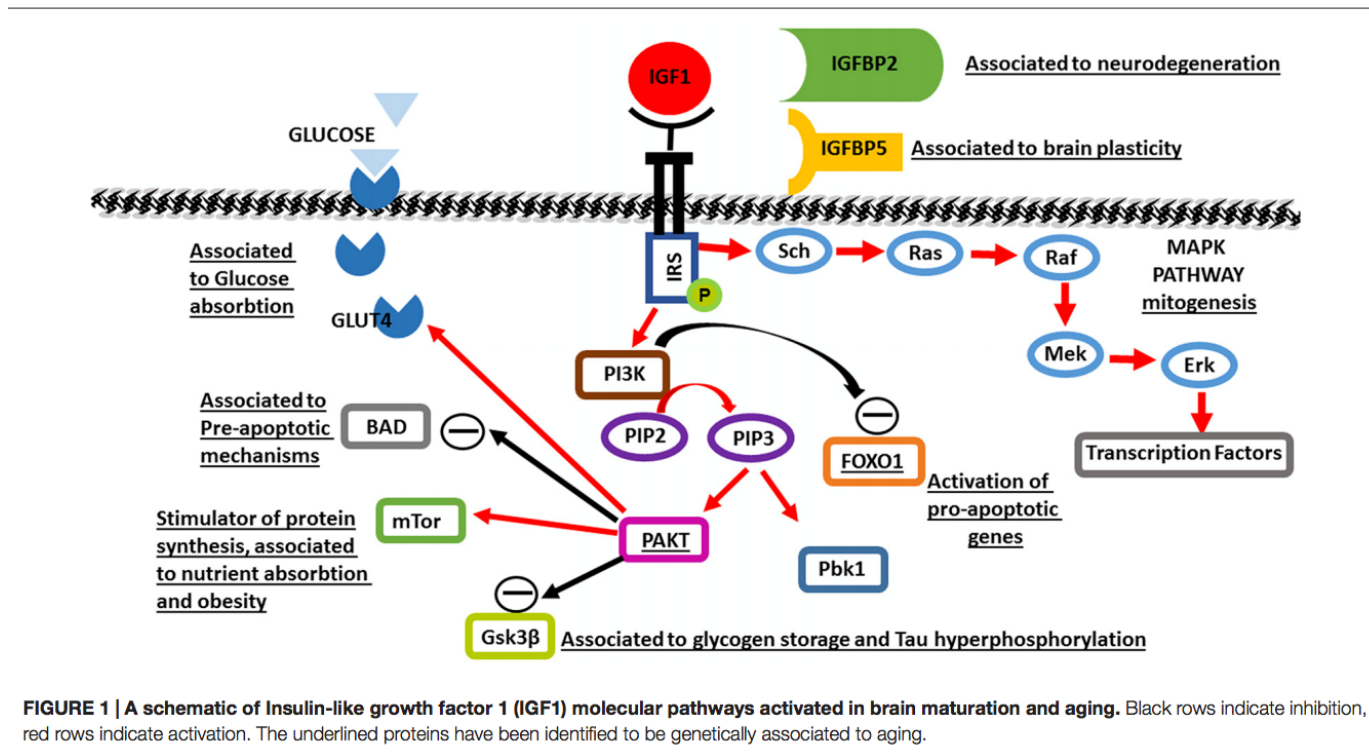
- Cognitive domains is grouping them as either “crystallized” or “fluid” intelligence
- Crystallized intelligence generally refers to vocabulary and long-term memory
- Fluid intelligence includes short term memory and active problem-solving and demonstrates a more marked age-related decline
- Several studies have shown a correlation between plasma IGF-I concentrations and performance on tests of fluid intelligence , suggesting that GH may play a role in maintenance of fluid intelligence.

# GH – Brain GH Bleed!!!

- overexpression of growth hormone were the most fearful, assessed by how long they froze after hearing the tone. Blocking the cell receptors that interact with ghrelin or growth hormone reduced fear to normal levels in chronically stressed rats
- amygdalar growth hormone levels also went up, and fearful memories were encoded more strongly.
- ghrelin levels remain high long after the chronic stress end



# IGF-1 Pathways



**FIGURE 1 | A schematic of Insulin-like growth factor 1 (IGF1) molecular pathways activated in brain maturation and aging.** Black rows indicate inhibition, red rows indicate activation. The underlined proteins have been identified to be genetically associated to aging.

# IGF-1

- Insulin-like growth factor 1 (IGF1) is a polypeptide hormone structurally similar to insulin. It is central to the somatotrophic axis, acting downstream of growth hormone (GH). Activates both the mitogen-activated protein (MAP) kinase and PI3K signaling pathways, acting in almost every tissue in the body to promote tissue growth and maturation through upregulation of anabolic processes.
- Remember local and systemic IGF produced and local is internal with receptor systemic has to bind to receptor and be internalized
- Neurotrophic effects of IGF1 signaling, giving evidence for promotion of neurogenesis, development and maturation, myelination, prolonged survival and resistance to injury

## IGF1 AND THE ADULT BRAIN: ADULT NEUROGENESIS

- IGF1 expression levels decrease again later in life, again at a time that corresponds with a decrease in hippocampal neurogenesis.
- low-dose IGF1 treatment triggered a small increase in the differentiation of neuronal progenitors into neurons.
- IGF1 signaling is key in promoting organized adult hippocampal neurogenesis
- IGF1 not only promotes adult neurogenesis through increased stem cell proliferation, also through organized cell migration
- **Exercise most extensively studied**, and recent studies show that this effect is mediated through IGF1 signaling

# IGF-1 Brain

- reduced IGF1 signaling is linked to cognitive dysfunction. Studies in humans found a significant correlation between better perceptual motor performance, information processing speed and fluid intelligence and higher circulating IGF1 levels
- **contradictory** with some studies reporting that reduced IGF1 signaling is neuroprotective, while others claim that reduced IGF1 signaling with age contributes to brain aging
- IGF1 appears to act in concert with BDNF and other neurotrophic factors to promote neurogenesis and remodeling in the brain

# DIHEXA



- Oligopeptide variant derived from angiotensin IV
- Permeates Blood Brain Barrier
- Improves cerebral blood flow
- Neuroprotective
  - Reverses scopolamine-dependent spatial learning deficits
  - Improves spatial learning in aged rats
  - Induces spinogenesis in cultures hippocampal neurons



McCoy AT, et al. Evaluation of metabolically stabilized angiotensin IV analogs as procognitive/antidementia agents. *J Pharmacol Exp Ther.* 2013;344:141–154.

Benoist CC, et. al. The Procognitive and Synaptogenic effects of Angiotensin IV- Derived Peptides are Dependent on Activation of the Hepatocyte Growth Factor/c-Met System. *J. Pharmacol Exp Ther.* 2014 Nov;351(2):390-402.

***Dihexa reported to be 7X more potent than BDNF (stimulating hepatocyte growth factor HGF), indicating it could possibly help in the repair of the brain and nerves in neurological disease.***

[J Alzheimers Dis. 2015;45\(4\):985-1000. doi: 10.3233/JAD-142814.](#)

### **The Brain Hepatocyte Growth Factor/c-Met Receptor System: A New Target for the Treatment of Alzheimer's Disease.**

[Wright JW<sup>1</sup>](#), [Harding JW<sup>1</sup>](#).

 **Author information**

Wright JW, Harding JW. The Brain Hepatocyte Growth Factor/c-Met Receptor System: A New Target for the treatment of AD. J Alzheimers Dis. 2015;45(4):985-1000.

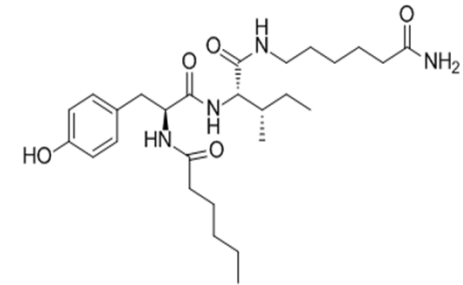
#### **Abstract**

Alzheimer's disease (AD) is a progressive neurodegenerative disease increasing in frequency as life expectancy of the world's population increases. There are an estimated 5 million diagnosed AD patients in the U.S. and 16 million worldwide with no adequate treatment presently available. New therapeutic approaches are needed to slow, and hopefully reverse, disease progression. This review summarizes available information regarding an overlooked therapeutic target that may offer a treatment to slow and hopefully halt AD, namely the hepatocyte growth factor (HGF)/c-Met receptor system. Activation of the c-Met receptor stimulates mitogenesis, motogenesis, morphogenesis, the ability to mediate stem cell differentiation and neurogenesis, and protects against tissue insults in a wide range of cells including neurons. This growth factor system has recently been shown to induce dendritic arborization and synaptogenesis when stimulated by a newly developed angiotensin-based analogue, N-hexanoic-Tyr-Ile-(6) amino hexanoic amide (Dihexa). This small molecule was derived from the pre-prototype molecule Nle1-angiotensin IV and has shown promise in facilitating the formation of new functional synaptic connections and augmenting memory consolidation in animal models of AD. Dihexa is a first-in-class compound that is orally active, penetrates the blood-brain barrier, and facilitates memory consolidation and retrieval. This angiotensin-based small molecule may be efficacious as a treatment for AD.

# DIHEXA



- Uses:
  - Cognitive support
  - Neuroprotection
  - Alzheimer's and dementia support
  - Parkinson's disease
  - Improving focus and mental performance
- Available as CREAM oral CAPSULE
- Cream = 20mg/ml 30ml applicator
  - Apply 0.5-1ml (2-4 clicks) to inner forearm daily – rub into until absorbed
- Capsule = 10mg, 20mg oral cap
  - 1-2 caps daily (10-40mg)
- SE's can include nervousness/irritability



Benoist CC, et. al. The Procognitive and Synaptogenic effects of Angiotensin IV- Derived Peptides are Dependent on Activation of the Hepatocyte Growth Factor/c-Met System. *J. Pharmacol Exp Ther.* 2014 Nov;351(2):390-402.

**SEMAX**  
NEUROPEPTIDE



- N-acetyl semax
- Met-Glu-His-Phe-Pro-Gly-Pro
- Russian developed originally
- Synthetic analog of ACTH fragments 4-10
- Neuroprotective
  - Promotes neuron survival
  - Affects carboxypeptidase -
  - Decreases glutamate neurotoxicity
  - Increased mitochondrial stability
  - Improves trophic supply to brain
  - Decreases effects of oxidative stress
  - Protects optic nerve



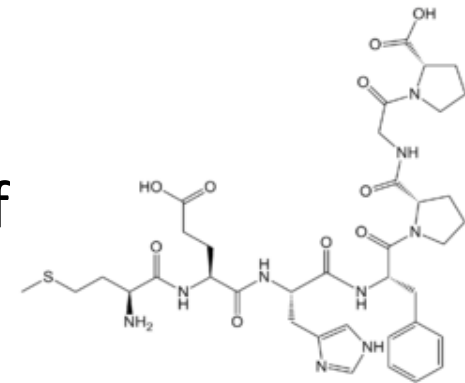
**SEMAX**

Storozhevskiy TP, et al. Effects of semax and its Pro-Gly-Pro fragment on calcium homeostasis of neurons and their survival under conditions of glutamate toxicity. Bull Exp Biol Med. 2007;15:601–604.





- Cognitive enhancement; increased concentration
- Anxiolytic
  - No addiction potential or “hangover” effects
- Analgesic at higher dosages (> 0.5mg/kg)
- May also increase physical performance and adaptation capacities in exposure to high intensity exercise



**SEMAX**  
NEUROPEPTIDE



- Dosage
  - SQ injection
  - 300 – 1,000 mcg daily OR 2 x weekly
  - More often leads to desensitization

**DSIP**

DELTA SLEEP INDUCING PEPTIDE



- Delta Sleep-Inducing Peptide
- Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu
- Naturally occurring somnogenic nonapeptide – peptide neuromodulator
- Readily crosses BBB
- Sleep promoting factor isolated from rabbit cerebral venous blood in 1977
- Found also in human brain
- Follows circadian rhythm – DSIP lower in morning, higher in afternoon/evening



**DSIP**

Miller LH, Turnbull BA, Kastin AJ, et. al. Sleep-Wave Activity of a Delta Sleep-Inducing Peptide Analog Correlates with its Penetration of the Blood-Brain Barrier. *Sleep*. 1986;9(1):80-4

# DSIP

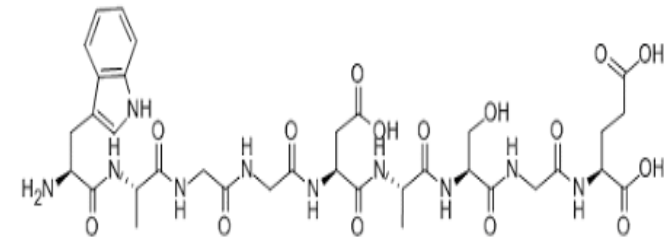
DELTA SLEEP INDUCING PEPTIDE



- GABAergic, glutamatergic

- Major Uses:

- Sleep promotion
- Neuroprotection



- Alcohol/drug detoxification and withdrawal

- DSIP increases “pressure” to sleep

- Sedation in the classical pharmacological sense is not seen with DSIP
- No side effects

Monti JM, et al. Study of delta sleep-inducing peptide efficacy in improving sleep on short-term administration to chronic insomniacs. *Int J Clin Pharmacol Res.* 1987;7:105–110.

**DSIP**

DELTA SLEEP INDUCING PEPTIDE



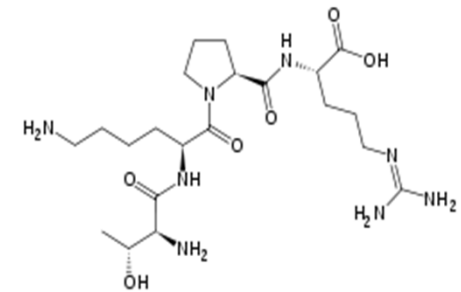
- Dosages - SubQ
  - 1mg/ml 3ml vial
  - 0.1ml (100mcg) SQ daily
  - Does not have to be administered at bedtime for clinical effectiveness
- No tolerance noted

Ji AX, Li CX, Ye YH *et al.* Synthesis of delta sleep-inducing peptide (DSIP) and its physiological activity. *Sci Sin [B]*.1983;26:174–185

# Peptide Cognitive Support - Selank

## SELANK

- Synthetic analogue of human immuno-peptide **tuftsin**
- Anxiolytic
  - Affects GABAergic system (GABA<sub>A</sub>)
  - No addiction potential or “hangover” effects
- Supports cognitive function (nootropic effect)
- Commonly used concurrently with Semax



## Supplied

5mg and 10mg vials lyophilized powder for reconstitution

## DOSAGE

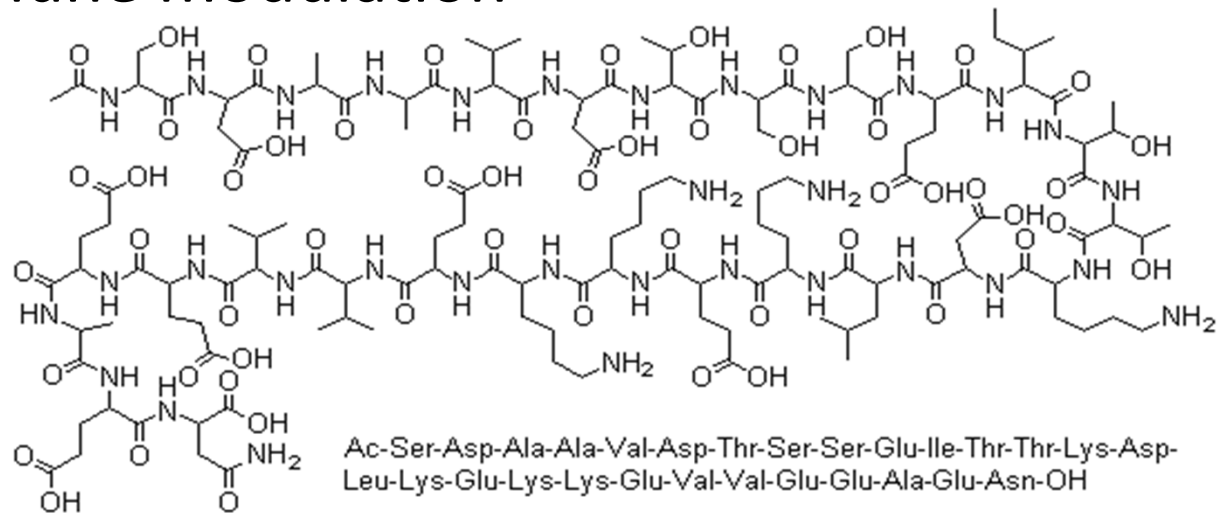
300-1000mcg, daily SQ or 2 times weekly alternating with Semax

## Nasal drops 0.15% 3ml

- 2-3 drops (400- 600 mcg) each nostril, 2-3 times daily
- Intranasal good for immediate relief of anxiety issues
- Responses can be immediate

# Thymosin Alpha 1

- Synthetic thymic peptide
- 28 amino acids
- MW = 3108.28
- Modulates innate immunity
- Pleiotropic immune modulation



Yang X, Qian F, He H, et al. Effect of thymosin alpha-1 on subpopulations of Th1, Th2, Th17 and regulatory T cells (Tregs) in vitrol. *Braz J Med Biol Res.* 2012;45(1):25-32.

Romani L, Moretti S, Fallarino F, et al. Jack of all trades: thymosin alpha-1 and its pleiotropy. *Ann NY Acad Sci.* 2012;1269:1-6.

# Thymosin Alpha 1

- Promotes T cell differentiation and maturation
  - In vivo and in vitro data
- Decreases T cell apoptosis
- Improves Th1 responses
- Balances Th1/Th2
- Activates indoleamine 2,3-dioxygenase enzyme
- Dampens immunity

Yang X, Qian F, He H, et al. Effect of thymosin alpha-1 on subpopulations of Th1, Th2, Th17 and regulatory T cells (Tregs) in vitro. *Braz J Med Biol Res.* 2012;45(1):25-32.

Romani L, Moretti S, Fallarino F, et al. Jack of all trades: thymosin alpha-1 and its pleiotropy. *Ann NY Acad Sci.* 2012;1269:1-6.



# Thymosin Alpha 1

- Decreases immune senescence
- Improves CD3+, CD4+, CD8+
- Improves production of IL-1 beta, IFN- $\gamma$ , IL-2, IL-3, IL-6, IL-10
- Improves NK cell activity and TNF-alpha
- Inhibits viral replication
- Antioxidant

Yang X, Qian F, He H, et al. Effect of thymosin alpha-1 on subpopulations of Th1, Th2, Th17 and regulatory T cells (Tregs) in vitrol. Braz J Med Biol Res. 2012;45(1):25-32.

Romani L, MorettiS, Fallarino F, et al. Jack of all trades: thymosin alpha-1 and its pleiotropy. Ann NY Acad Sci. 2012;1269:1-6.

# Thymosin Alpha 1

- Enhances dendritic cells
- Enhances antibody responses
- Blocks steroid-induced apoptosis of thymocytes
- Anti-tumor effects
- Protection against oxidative damage

Goldstein AL. History of the discovery of the thymosins Ann N Y Acad Sci. 2007;1112: 1– 13.

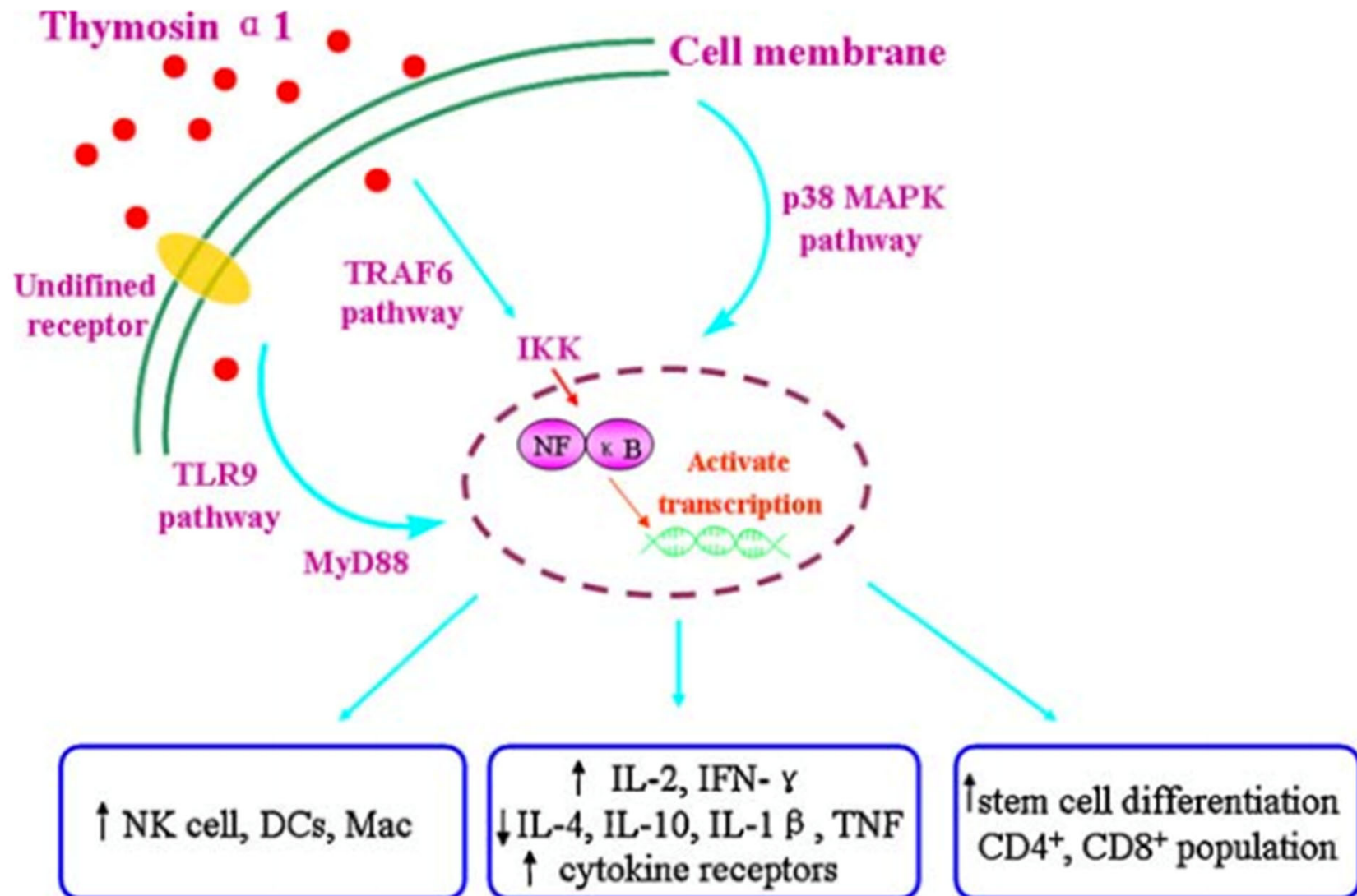
Giuliani C, Napolitano G, Mastino A *et al.* Thymosin-alpha1 regulates MHC class I expression in FRTL-5 cells at transcriptional level. Eur J Immunol 2000; **30**:778–86.

# Th1 Th2 Imbalance

**Studies report immune dysfunction is associated with a wide-variety of common chronic illnesses**


- Chronic Stress
- Depression
- Metabolic Syndrome
- Weight management issues
- Insulin resistance and type 2 diabetes
- Anti-Aging effects – increased oxidative stress
- Chronic fatigue syndrome/fibromyalgia
- Autoimmune conditions
- Cancer
- Chronic
- Environmental toxins
- Chronic infections, including Lyme, viruses, candida and many parasites
- Glutathione depletion consistently results in TH1-TH2 shift
- Dysbiosis
- Food allergies or sensitivities
- Zinc and selenium deficiencies

# Ta1 Mechanism



# Thymosin Alpha 1 COVID-19

ACCEPTED MANUSCRIPT

**Thymosin alpha 1 (T $\alpha$ 1) reduces the mortality of severe COVID-19 by restoration of lymphocytopenia and reversion of exhausted T cells** 

Yueping Liu, Yue Pang, Zhenhong Hu, Ming Wu, Chenhui Wang, Zeqing Feng, Congzheng Mao, Yingjun Tan, Ying Liu, Li Chen ... [Show more](#)

[Author Notes](#)

\*\*\* Most COVID-19 cases display severe lymphocytopenia, especially in aged and severe cases \*\*\*

# Thymosin Alpha 1 COVID-19

- May 2020 clinical study - General Hospital of the Central Theatre Command and Wuhan Pulmonary Hospital in Wuhan, CHINA
- 76 severe cases of COVID-19
- Admitted into Hospital from Dec 2019 – March 2020
- Thymus output and peripheral blood mononuclear cells PMBCs were measured
- T cell exhaustion markers on CD8+ cells also measured
  - PD-1
  - Tim-3
- Administered 10mg/ml, 1ml SQ Tα1 X 7 days (some more days tx)

Liu Y, et al. Thymosin alpha 1 (Ta1) reduces the mortality of severe COVID-19 by restoration of lymphocytopenia and reversion of exhausted T cells.

# Thymosin Alpha 1 COVID-19

## RESULTS:

- Tα1 reduced the mortality of severe COVID-19
  - By restoration of lymphocytopenia and reversion of exhausted T cells
  - 11.11% vs. 30%
- COVID-19 patients with the counts of CD8+ or CD4+ T cells lower than 400/μL or 650/μL, respectively, gain more benefits
- Tα1 also successfully restores CD8+ and CD4+ T cell numbers in aged patients

Liu Y, et al. Thymosin alpha 1 (Ta1) reduces the mortality of severe COVID-19 by restoration of lymphocytopenia and reversion of exhausted T cells.

# Thymosin Alpha 1 COVID-19

## AUTHORS CONCLUDED:

- Tα1 supplement significantly reduce mortality of severe COVID-19 patients, especially in those with CD8+ and CD4+ lower than 400ul or 650um respectively
- Tα1 reverses T cell exhaustion and recovers immune reconstitution through promoting thymus output during SARS-CoV-2 infection.

Liu Y, et al. Thymosin alpha 1 (Ta1) reduces the mortality of severe COVID-19 by restoration of lymphocytopenia and reversion of exhausted T cells.



# Ta1 Applications

- Conditions requiring immune response modulation
- Hepatitis B and C
- Treatment of HIV/AIDS
  - Can be used in conjunction with oral antiretroviral treatments
- Cancer treatment/chemotherapy adjunct
  - Non-small cell lung, hepatocellular, malignant melanoma
- DiGeorge's Syndrome

Rasi G, Terzoli E, Izzo F, et al. Combined treatment with thymosin alpha 1 and low-dose interferon alpha after dacarbazine in advanced melanoma. *Melanoma Res.* 2000;10:189-192.

Matteucci C, Grelli S, Balestrieri E, et al. Thymosin alpha 1 and HIV-1: recent advances and future perspectives. *Future Microbiol.* 2017;12:141-155.

# Ta1 Applications

- Depressed response to vaccinations
- Lyme disease
- Chemo attractant stimulation
- Adjunct to flu vaccines especially in geriatrics
- Chronic inflammatory conditions – autoimmunity
  - CFS/Fibromyalgia

# Ta1 Applications

- Sepsis
- May reduce hematological toxicity of cytotoxic drug therapies
  - Cyclophosphamide
  - 5-fluorouracil (5FU)
  - Dacarbazine
  - Ifosfamide

Liu D, et al. The efficacy of thymosin alpha 1 as immunomodulatory treatment for sepsis: a systematic review of randomized controlled trials. *BMC Infect Dis.* 2016;16:488.

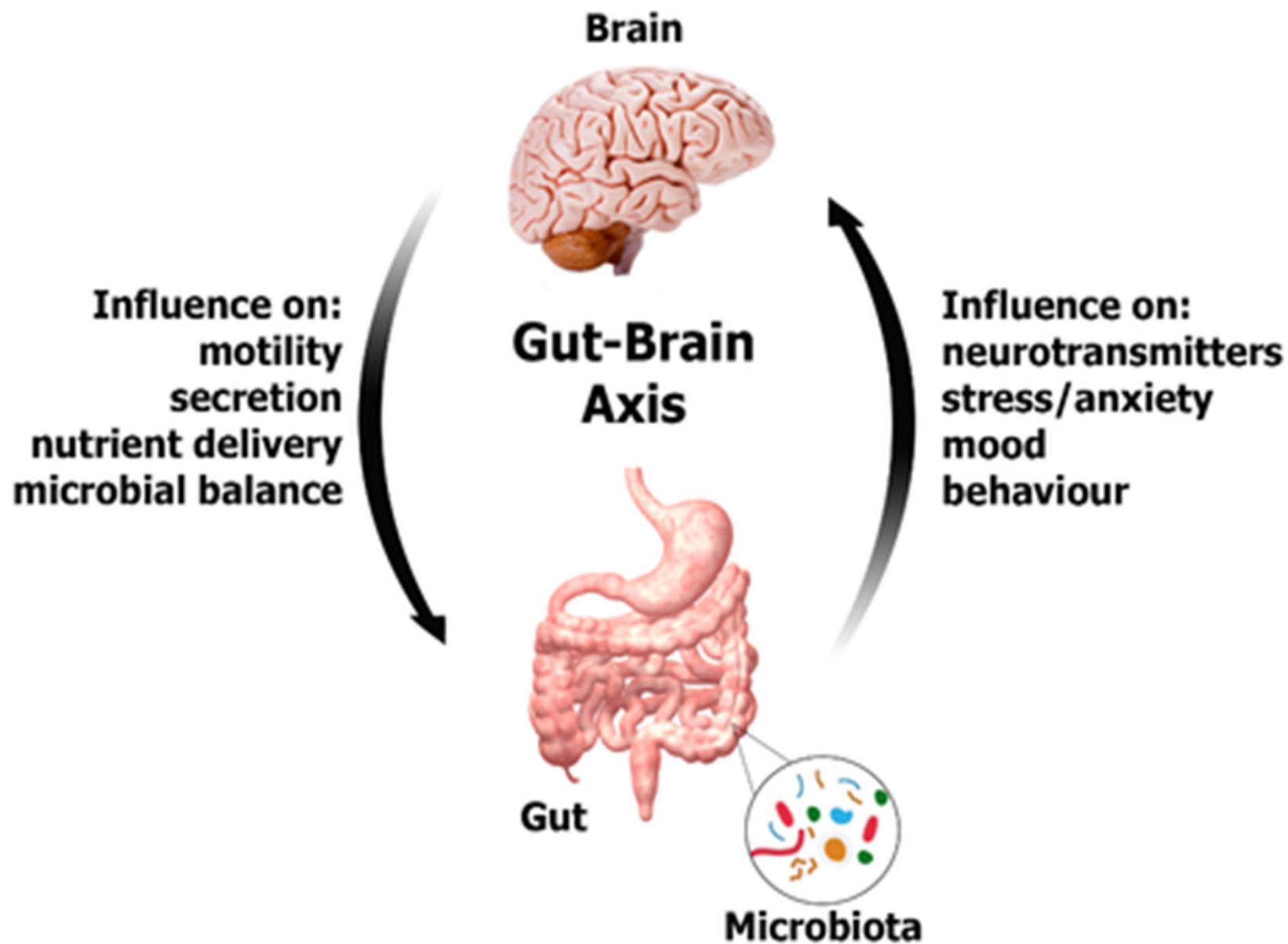
An TT, et al. [Primary assessment of treatment effect of thymosin alpha 1 on chemotherapy-induced neurotoxicity. *Ai Zheng* . 220004; 23(Suppl):1428-30.

# Ta1 Dosage

- 3mg/ml 5ml vial
- 450mcg (0.15ml) SQ 1-2 x daily OR 1.5 mg (0.5 ml) SQ every 3<sup>rd</sup> day
- Treatment from 2 weeks for viral infection and 3 months or longer for HIV/ cancer / Hepatitis B, C or complicated immune suppression or over-activation
- Multiple overlap of usage
- Transient increases in ALT have been reported to occur
- Do not use in individuals being deliberately immunosuppressed.

Yang X,, et al. Effect of thymosin alpha-1 on subpopulations of Th1, Th2, Th17 and regulatory T cells (Tregs) in vitrol. Braz J Med Biol Res. 2012;45(1):25-32.







# BPC 157 and Colovesical Fistulas – RAT study

**COLOCUTANEOUS FISTULAS**  
**4 WEEKS**  
28d-C

**+ 2 WEEK SALINE**  
**(5ml/kg IP/once daily)**  
**CONTROLS (C)**

**BPC 157 THERAPY**  
**THROUGHOUT**  
**THE NEXT 2 WEEKS**

**EXTERNAL FISTULAS HEALING**

**COLOCUTANEOUS FISTULA**  
**AT POST-OPERATIVE DAY 28 (28d)**  
**+ 2 WEEK SALINE (5ml/kg IP/once daily) CONTROLS (C)**

**HEALING OF THE ONE-MONTH-ESTABLISHED**  
**RAT COLOCUTANEOUS FISTULA WITH**  
**THE BPC 157 THERAPY THROUGHOUT THE NEXT**  
**2 WEEKS.**

**6 WEEKS**

Grgic T, et al. Stable gastric pentadecapeptide BPC 157 heals rat colovesical fistula. Eur J Pharmacol. 2016;780:1-7.



# BPC 157

- Helps heal tissues
  - Reported to improve cell survival under oxidative stress
  - Increased fibroblast migration and dispersal
  - Induces F-actin formation in fibroblasts
  - Improves angiogenesis
  - Enhances vascular expression of VEGFR2
  - BPC-157 increases the extent of phosphorylation of paxillin and FAK proteins without affecting the amounts produced
- used in deep skin burns, corneal injuries
- injured muscle, tendon, ligament or bone

Duzel A, et al. Stable gastric pentadecapeptide BPC 157 in the treatment of colitis and ischemia and reperfusion in rats: new insights. *World J Gastroenterol.* 2017;23(48):8465-88.

# BPC 157

- Neuroprotective
  - Influences serotonergic, dopaminergic, opioid and GABAergic systems
  - Improves nerve regeneration
  - Decreases neuroinflammation
  - May help in depression
  - Ameliorates alcohol withdrawal symptoms and opposes alcohol intoxication

Sikiric P, et al. Brain-gut axis and pentadecapeptide BPC 157: Theoretical and practical implications. *Curr Neuropharmacol*. 2016;14:857-65.

# BPC 157

- Cardioprotective
  - May help regulate blood pressure
  - Nitric oxide improvement
  - BPC 157 rapidly and permanently counteracts the QTc prolongation induced by neuroleptics (such as haloperidol, fluphenazine, clozapine, olanzapine, quetiapine) and prokinetics

Strinic D, et al. BPC 157 counteracts QTc prolongation induced by haloperidol, fluphenazine, clozapine, olanzapine, quetiapine, sulpiride and metoclopramide in rats. *Life Sciences*. 2017;186(1):66-79.

Seiwerth S, et al. BPC157 and blood vessels. *Curr Pharm Des*, 2014;20(7):1121-35.

# BPC 157 -Dosage

- SubQ
  - Half life approx. 4 hours
  - 400 – 600 mcg/day total
  - If injury specific = split dosing into 20-300 mcg BID
  - Oral = 500 mcg daily
- Corticosteroids may reduce BPC-157's ability to heal muscles
- Results can be spontaneous and improve over 2-4 weeks treatment
- Safe in recommended dosages