Peptide Therapies in Endocrine Restoration

presented by :

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Clinical Director Pro Football Hall of Fame
Performance Health

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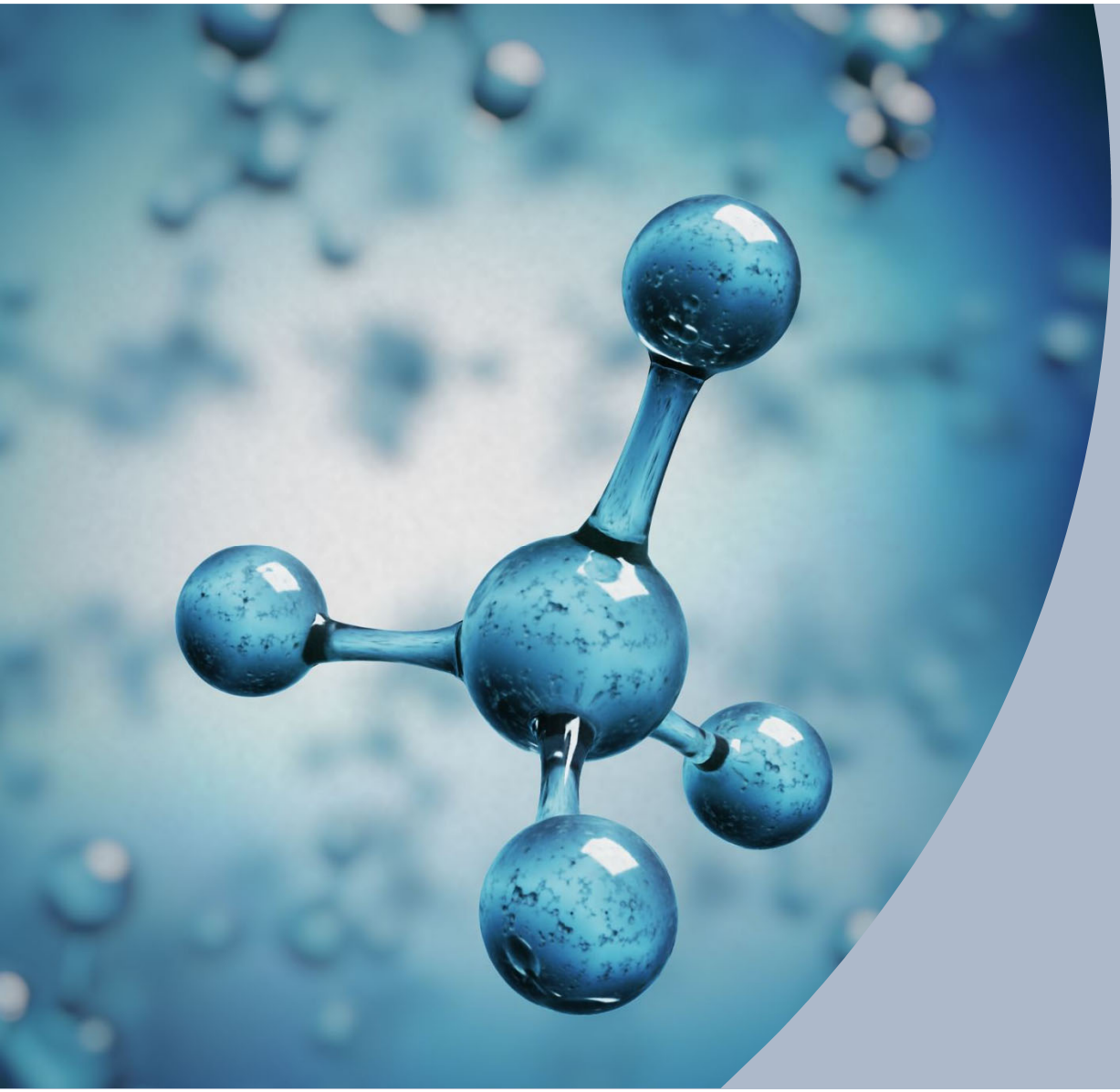


Background

Endocrine Support

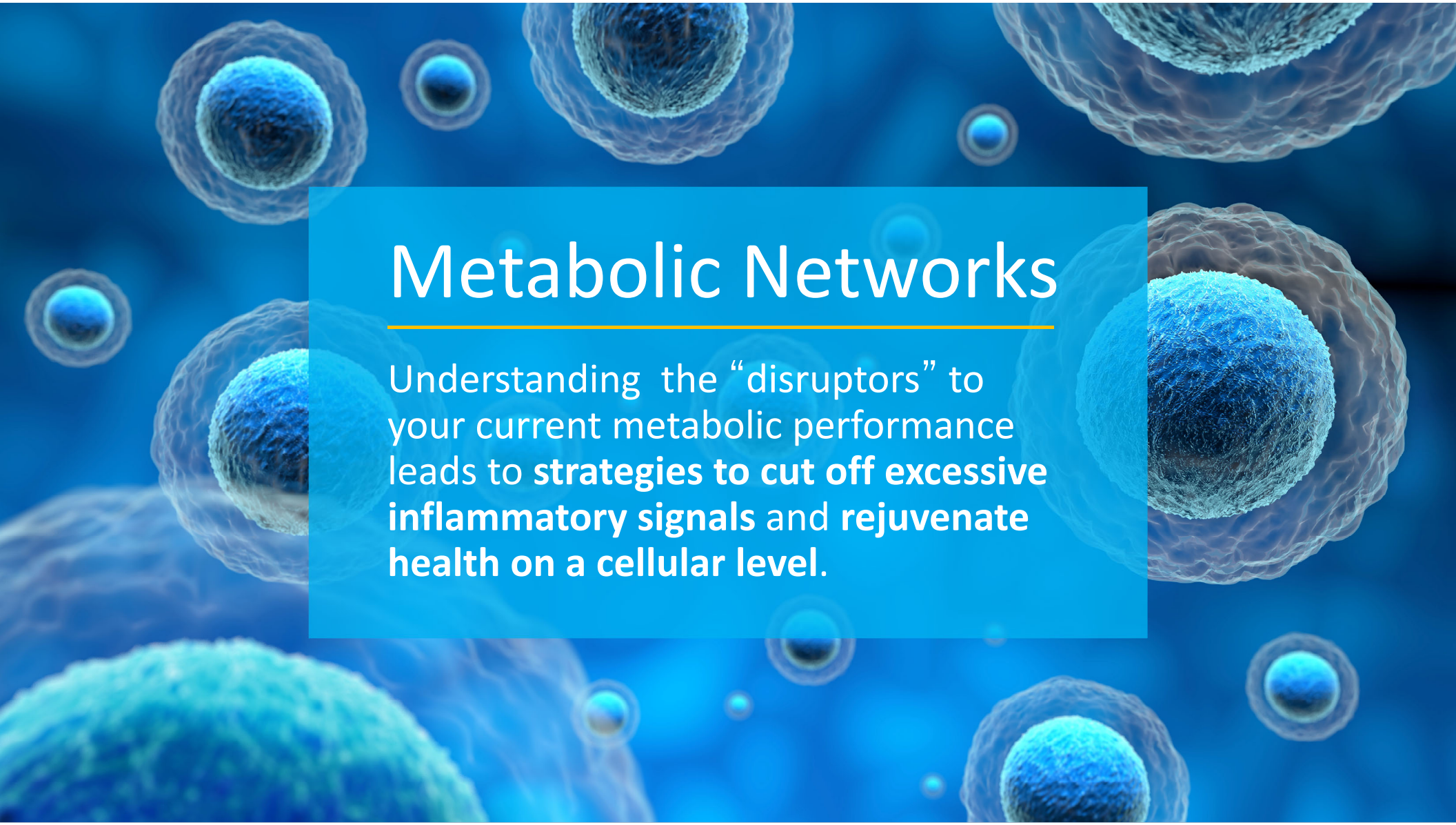
METABOLISM

The sum total of all the chemical reactions **driving how you feel today** and creating the chemistry **moving you toward future health**.

METABOLISM

Directly under the influence of Global Metabolic Inflammatory Signaling =

Metaflammation drives Metabolic Dysregulation


Metabolic Networks
Understanding the “disruptors” to your current metabolic performance leads to **strategies to cut off excessive inflammatory signals** and **rejuvenate health on a cellular level**.

Key Tenants of

Aging and Performance

- Oxidative Stress / Inflammation
- Hormonal Balance
- Stress Hormones
- Glucose / Insulin Regulation
- Immune Balance
- Environmental Burden
- Individuality

Metaflammation

- Also know as “Inflammageing” and metabolism induced inflammation
- Chronic low-grade inflammatory sequela
- Increases aging processes and metabolic signaling issues
- Caused by AND leads to “diabesity”:
  - Insulin resistance; type 2 diabetes
  - Obesity
  - Stress
  - Diet
  - LPS induced
  - Liver / kidney issues

Prattichizzo F, et al. Inflammageing and metaflammation: the yin and yang of type 2 diabetes. Ageing Res Rev. 2018;41:1-17.

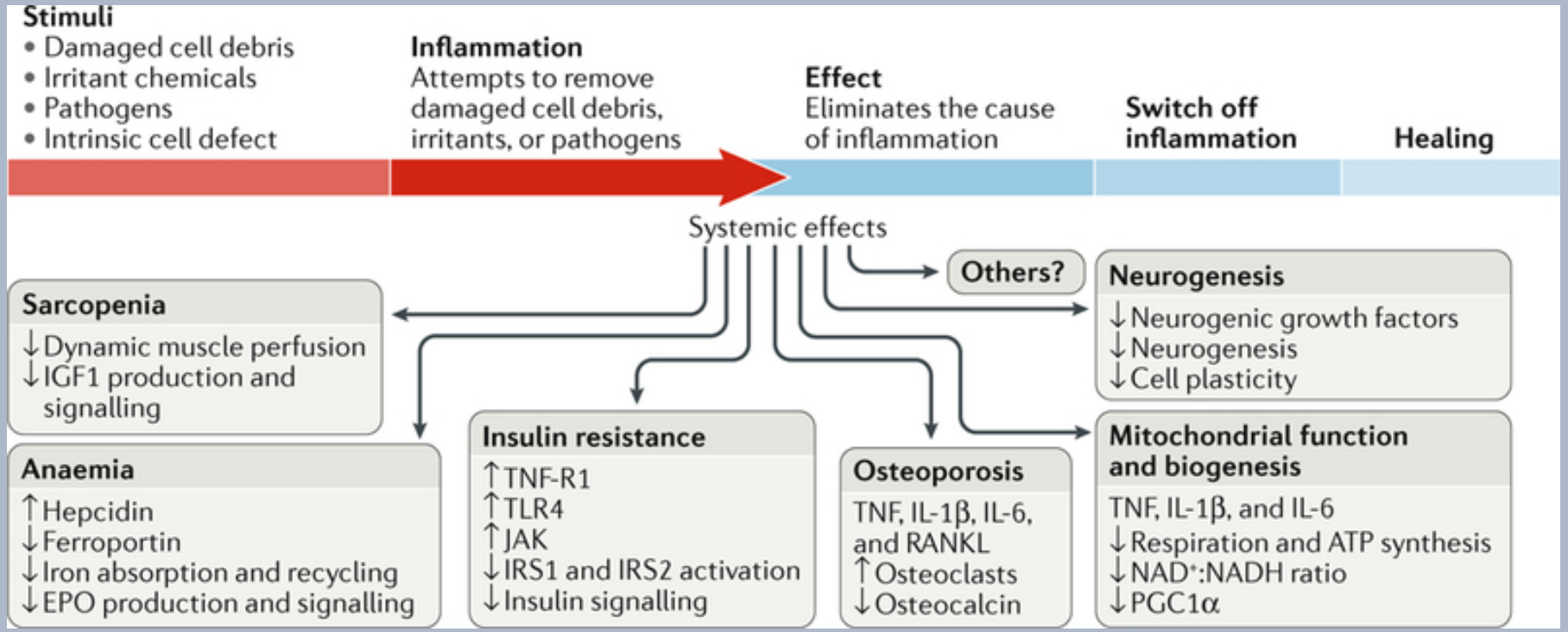
Metaflammation

Results in co-morbid conditions:

- Altered methylation patterns
- Cardiovascular issues – lipid, vascular
- Hormonal imbalances
- Liver and kidney diseases
- Immune dysfunction
- Sleep problems
- Cognitive and mood problems
- Sarcopenia
- Osteoporosis
- Cancer

Prattichizzo F, et al. Inflammageing and metaflammation: the yin and yang of type 2 diabetes. Ageing Res Rev. 2018;41:1-17.

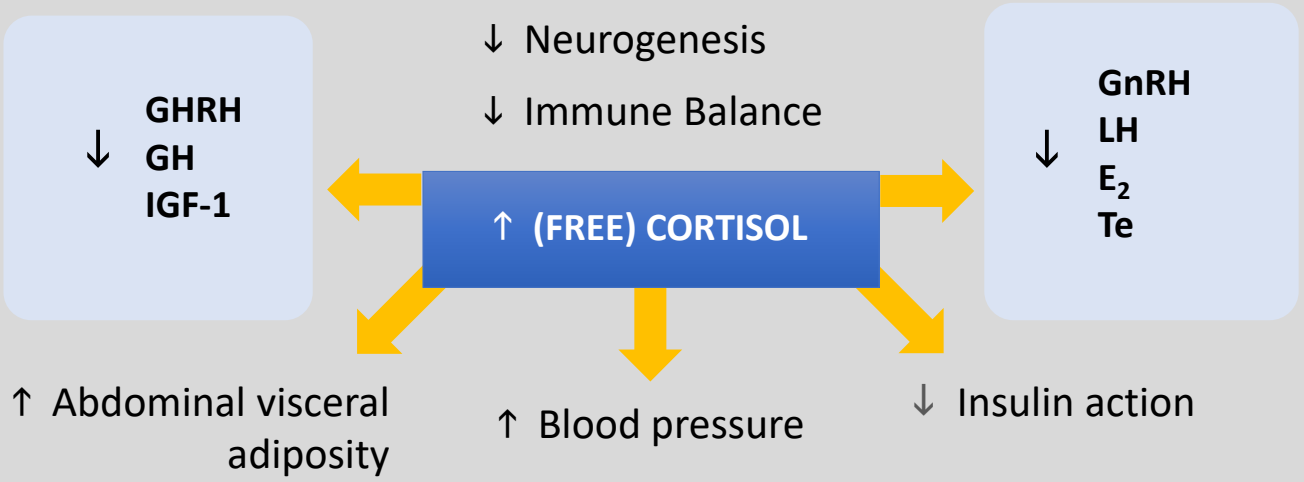
Metaflammation Induces Catabolic State



Ferruci L, et al. Inflammageing: chronic inflammation in ageing, cardiovascular disease and frailty. Nat Rev Cardiol. 2018;15(9):505-22.

Review

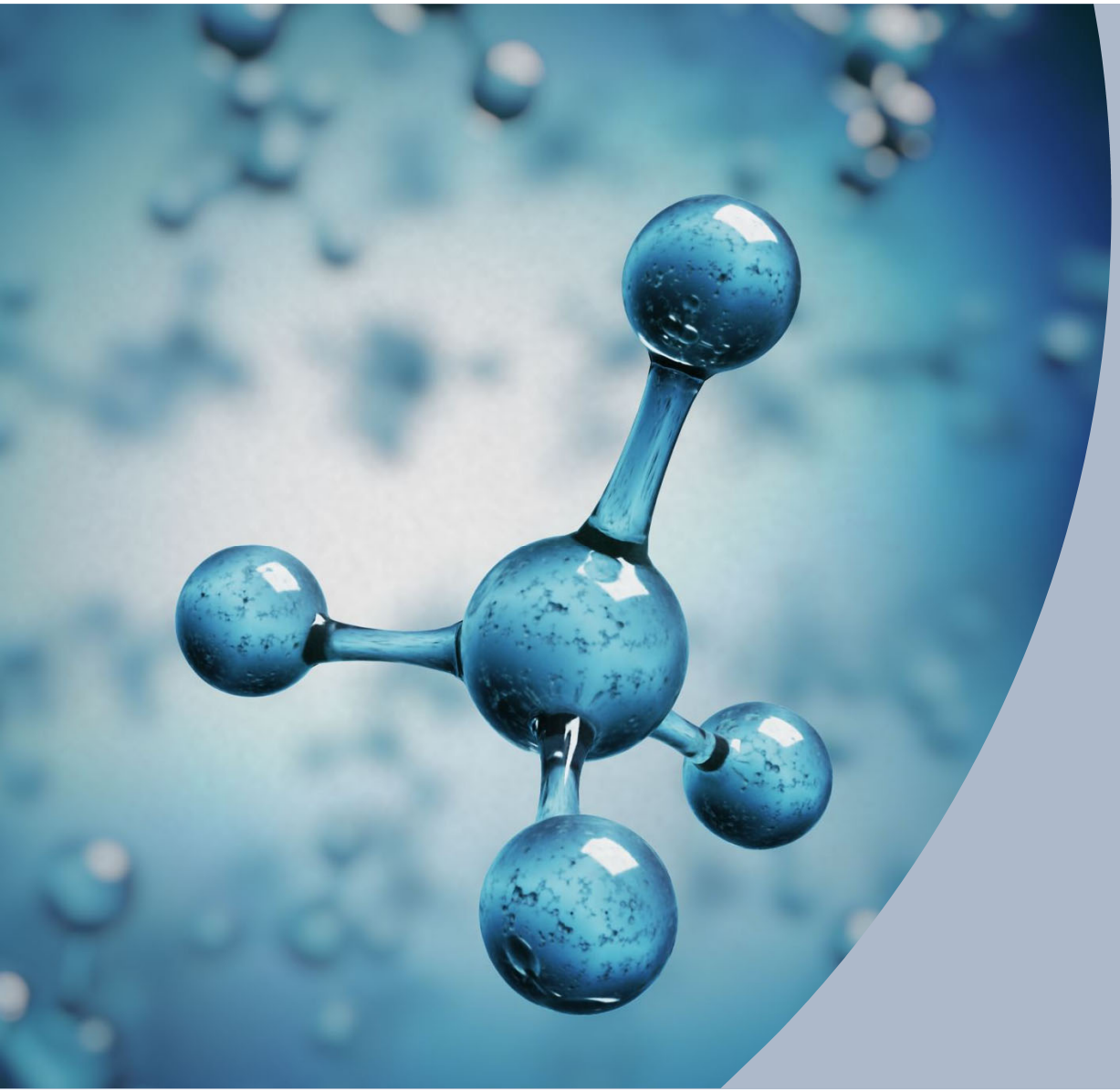
Clinical Effects of Excessive HPA axis Activation



OUTCOMES:

- (osteopenia, sarcopenia, syndrome X, cognitive decline, immunological compromise)
- (fractures, frailty, cardiovascular disease, memory loss, infectious complications)

Adapted from: Endocrinology and Metabolism Clinics of North America, Elsevier Publishing, ed. Anne R. Cappola. June 2013, vol. 42, no. 2.



Peptides

Endocrine Support

Exogenously Administered Peptide Roles in the Body

- Transport and storage of small molecules
- Coordinated motion via muscle contraction
- Mechanical support from fibrous protein
- Generation and transmission of nerve impulses
- Enzymatic catalyst
- Immune protection – antibody production
- Controls growth and differentiation of hormones

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
  - Interest by Pharma
- 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.

The Future

- FDA approval is increasing

- Specialty pharmacies that sequence peptides in-house increasing

  - Q/A testing – HPLC purification, mass spectrophotometry

  - Rx’s for peptide therapies now a reality

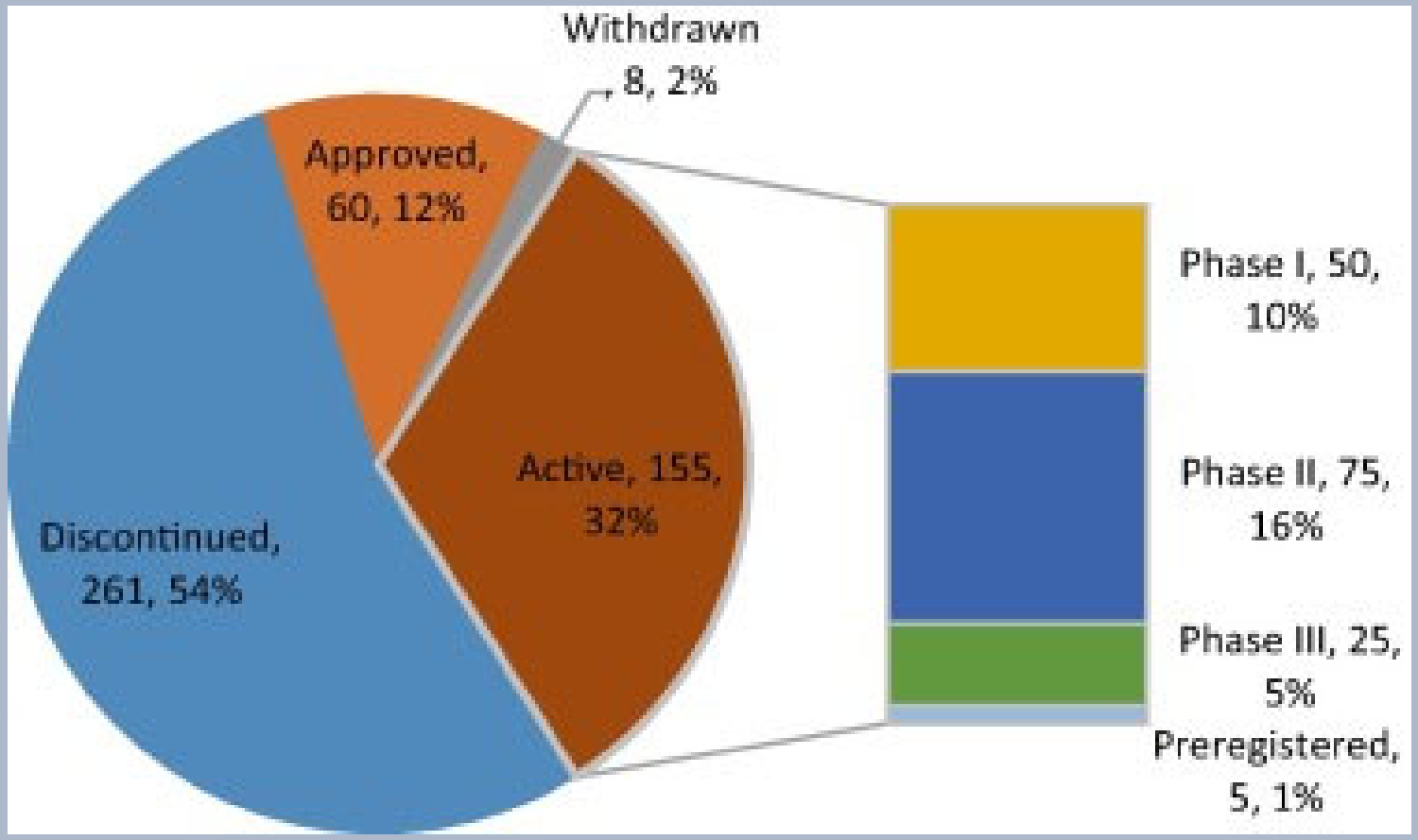
  - Tailor made to practitioner's specs and patients’ individual needs

Recent Advances

- Novel strategies
  - Allow for the modulation of pharmacokinetic properties
  - Target specificity through amino acid or backbone modification
  - Incorporation of non-natural amino acids - polymers
  - Conjugation of moieties that extend half-life or improve solubility – 30% of peptides in clinical trials
  - Improved cell penetration
  - Nanocarrier technology
  - Liposomal technology
  - Novel formulation strategies reduce injection frequency
  - Improved stability
  - Transdermal
  - Class B receptor targets

Galdiero S, et al. Peptide-based drugs and drug delivery systems. Molecules. 2017; 22(12):2185.
Herrero EP, Alonoso MJ, Csaba N. Polymer-based oral peptide nanomedicines. Ther Deliv. 2012;3(5):657-68.

Worldwide Statue of Therapeutic Peptides – 2018



Lau JL, et al. Bioorg Med Chem. 2018;26(10):2700-2797

Time to Embrace

- The environment and Landscape are quickly unfolding to embrace peptides as a mainstay in therapeutic options for acute and Chronic Conditions
  - Pathological inflammation , Brain and other organs
  - Blood glucose Regulation
  - Insulin control
  - Cardiac Disease
  - Metabolic Syndrome
  - Weight issue
  - Immune deficiencies including HIV/AIDS
  - Cancer Autoimmunity and Cancer
  - Bone & Joint problems
  - Sleep disorders

Journal of Medicinal Chemistry

Perspective

pubs.acs.org/jmc

The Current State of Peptide Drug Discovery: Back to the Future?

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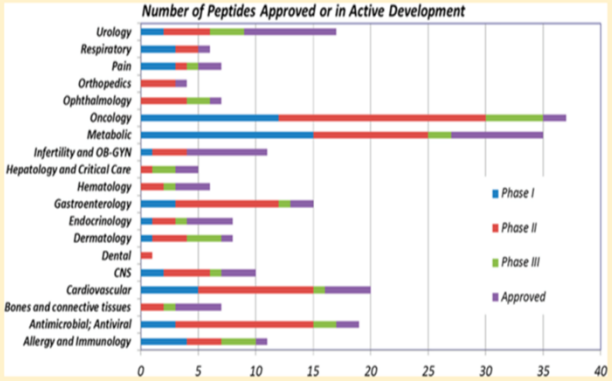
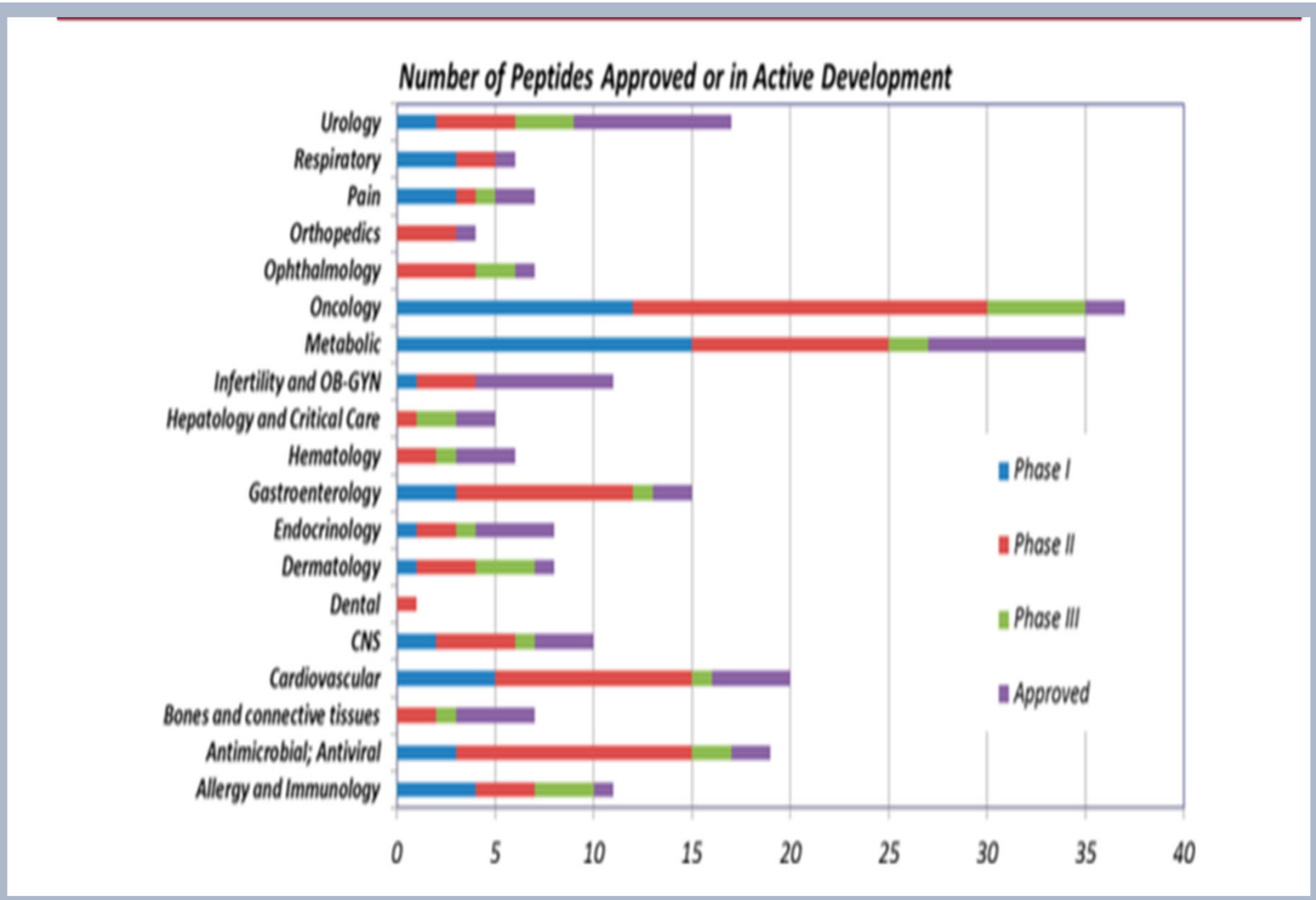
ABSTRACT: Over the past decade, peptide drug discovery has experienced a revival of interest and scientific momentum, as the pharmaceutical industry has come to appreciate the role that peptide therapeutics can play in addressing unmet medical needs and how this class of compounds can be an excellent complement or even preferable alternative to small molecule and biological therapeutics. In this Perspective, we give a concise description of the recent progress in peptide drug discovery in a holistic manner, highlighting enabling technological advances affecting nearly every aspect of this field: from lead discovery, to synthesis and optimization, to peptide drug delivery. An emphasis is placed on describing research efforts to overcome the inherent weaknesses of peptide drugs, in particular their poor pharmacokinetic properties, and how these efforts have been critical to the discovery, design, and subsequent development of novel therapeutics.

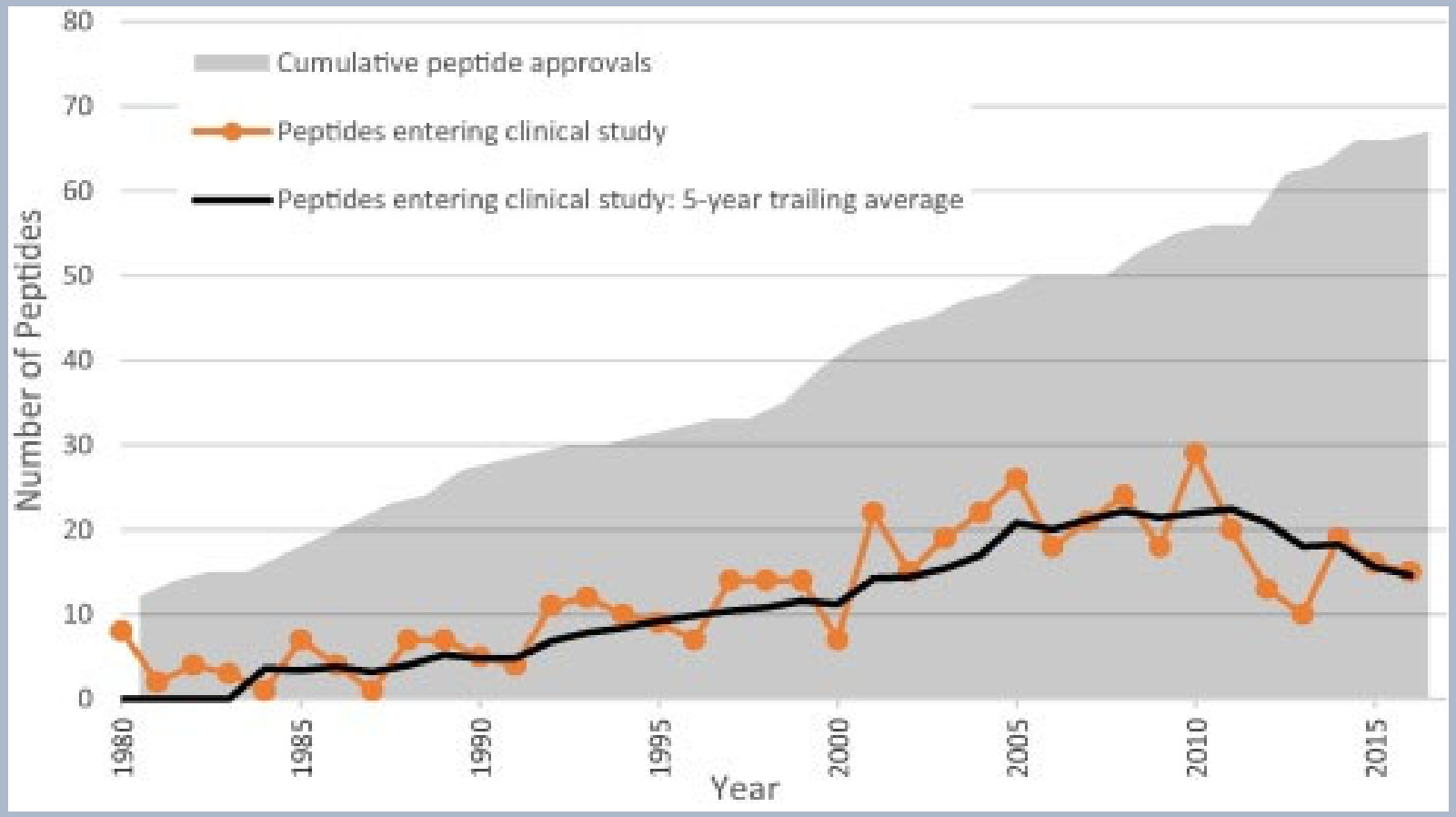


J. Med. Chem., 2018, 61 (4), pp 1382–1414



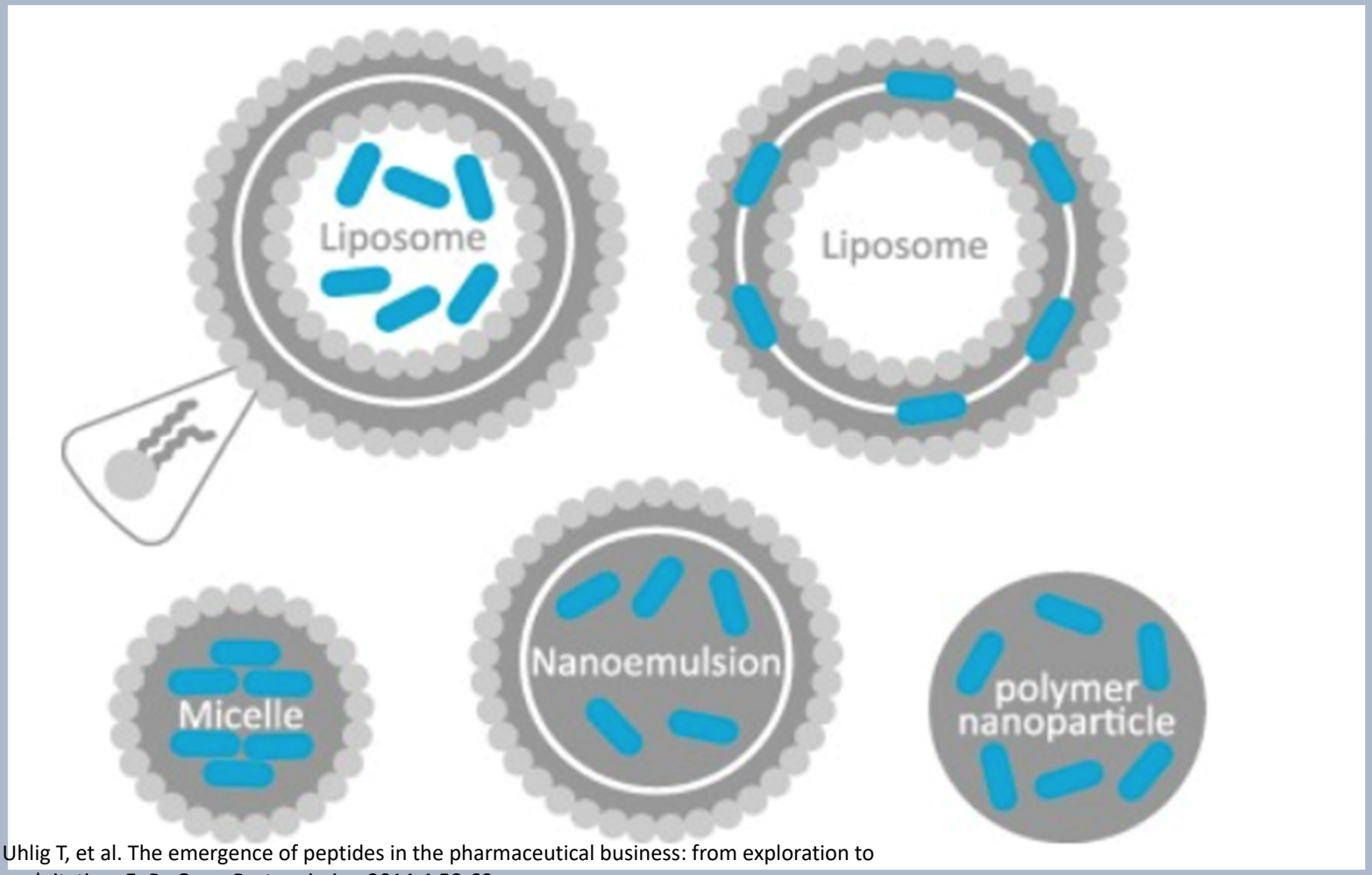
J. Med. Chem., 2018, 61 (4), pp 1382–1414

Peptides and Pharma



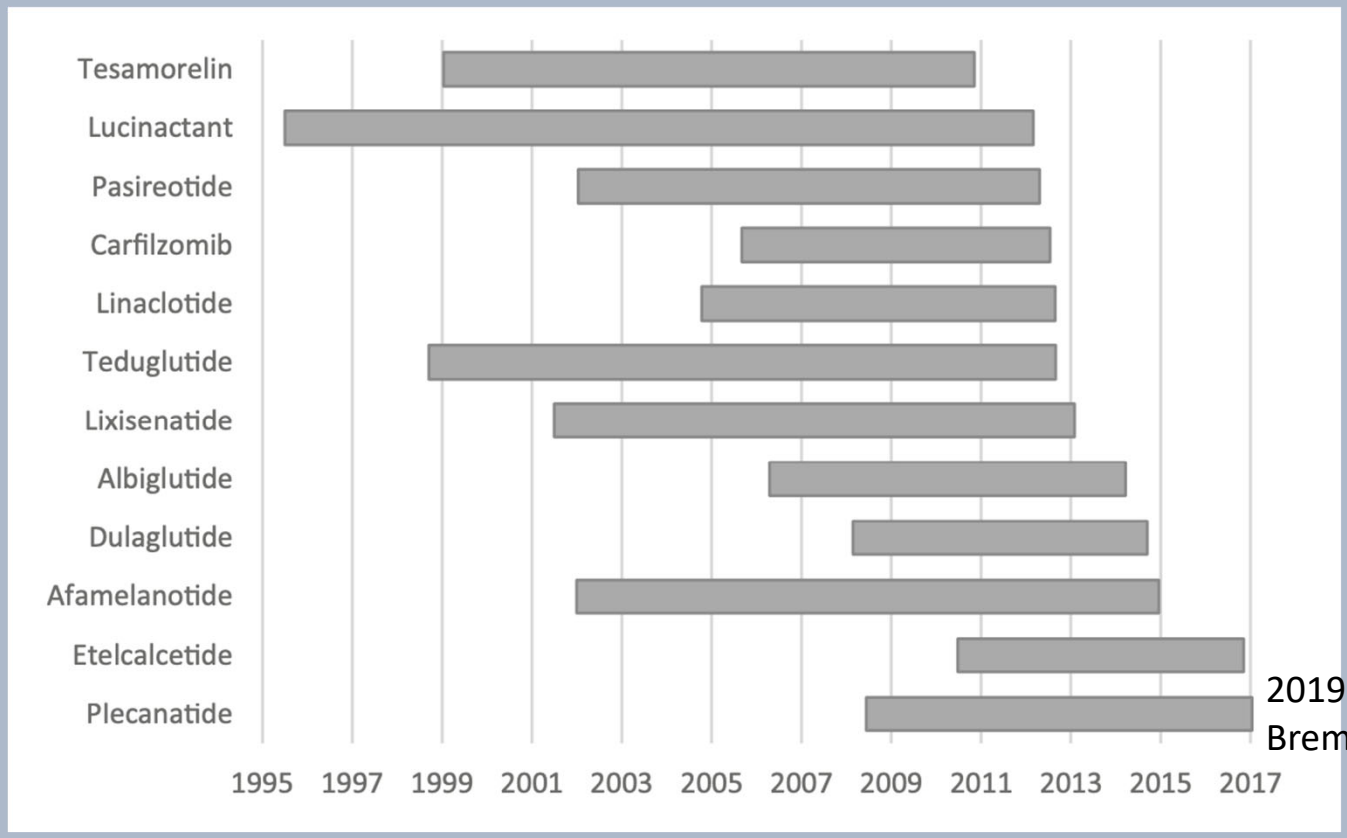
Lau JL, et al. Bioorg Med Chem. 2018;26(10):2700-2797

New Peptide Formulations



Uhlig T, et al. The emergence of peptides in the pharmaceutical business: from exploration to exploitation. EuPa Open Proteonimics. 2014;4:58-69.

Clinical Development - US Peptides Approved



2019
Bremelanotide

Lau JL, et al. Bioorg Med Chem. 2018;26(10):2700-2797

Potential Side Effects from Peptide Injections

- Itchy at the injection site
- Redness at the injection site
- Water retention - most likely need to reduce dose
- Increased hunger
- Dry mouth
- Nausea
- Tingling or numbness in the extremities (toes, fingers – reduce dose)
- Increased hair and nail growth

Less-Common Potential Side Effects from Peptide Injections – short and long term

- Increased tiredness and physical yawning
- Hypertension
- Liver and Kidney stress
- Kidney physical discomfort
- Darkening of moles and more freckling
- Joint pain
- Headaches – improve hydration
- Loss of fertility
- Increased prolactin
- Unintended weight loss or gain

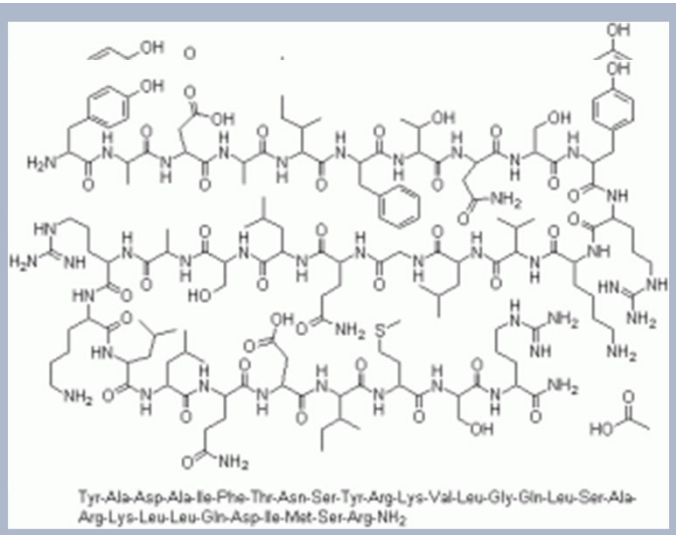
Quality

- Use only USA made peptides manufactured by qualified and Licensed Compounding Pharmacies
- 99% purity is best
- Highly pure = > 95%
- Don’t use less than 95%

Peptides in HRT Support

- Support Hypothalamic-Pituitary-Adrenal (HPA) axis and Hypothalamic-Pituitary-Gonadal (HPG) Axis Signaling
- Decreases effects of stress on HPA axis
- Improve sex hormonal levels
- Supports hGH levels
- Improve sexual desire/libido – melanocortin binding
- Supports harmonious metabolic signaling

Sermorelin



- Synthetic version of GHRH
- GFR 1-29
- Contains 29 amino acids
- Stimulates pituitary to release hGH
- Approved in 1991 by FDA for treatment of GH deficiency in children
- Increases IGF-1 in blood
- Enhances overall health and wellbeing

Prakash, Amitabh, and Karen L. Goa. "Sermorelin." *BioDrugs* 12.2 (1999): 139-157.

Sermorelin

- Long term effectiveness in Aging management
- Minimum of 6 months treatment protocol
- Can be used indefinitely
- Generally results are within first few months
  - Improved energy
  - Improved memory and cognition
  - Improved sexual performance
  - Increased bone density
  - Improved mood
  - Decreased body fat %
  - Thicker hair
  - Decreased cellulite and/or wrinkles
  - Improved recovery from illness or injury
  - Decreased inflammation – less muscle/joint aches, pain

Walker RF. Sermorelin: a better approach to management of adult-onset growth hormone insufficiency. Clin Interv Aging. 2006;1(4):307-8.

Sermorelin

- 200-300 mcg SQ daily 5-7 nights of week before bedtime on empty stomach
- Short half-life (approximately 8-12 minutes)
- Work into a multi-dosing protocol such as ipamorelin during the day, sermorelin at bedtime
- Efficacy decreases with time due to antibody production
- Bioconjugates with albumin can form altering therapeutic window - ↑ $T_{1/2}$

Walker RF. Sermorelin: a better approach to management of adult-onset growth hormone insufficiency. Clin Interv Aging. 2006;1(4):307-8.

CJC-1295/Ipamorelin

- CJC-1295 is MOD GRF (1-29) **WITH or WITHOUT** DAC (drug affinity complex)
- Modified growth hormone releasing factor
- DAC increases half- life
- Measurable concentration after 10-13 days
- >90% binding to serum albumin
- Elevates GH and IGF-1 for several days after single administration

Teichman SL, et al. Prolonged stimulation of growth hormone (GH) and insuiln like growth factor I secretion by CJC-1295, a long acting analog of GH-releasing hormone in healthy adults. J Clin Endocrinol. 2006;91:799-805.

CJC-1295/Ipamorelin Uses

- Improved physical performance
- Increased muscle mass
- Weight loss support
- Thermogenic – fat burning
- Improved recovery from exercise and injury
- Increased bone density
- Cardiovascular support
- Improved sex drive
- Neuroprotection
- Improved cognition and memory

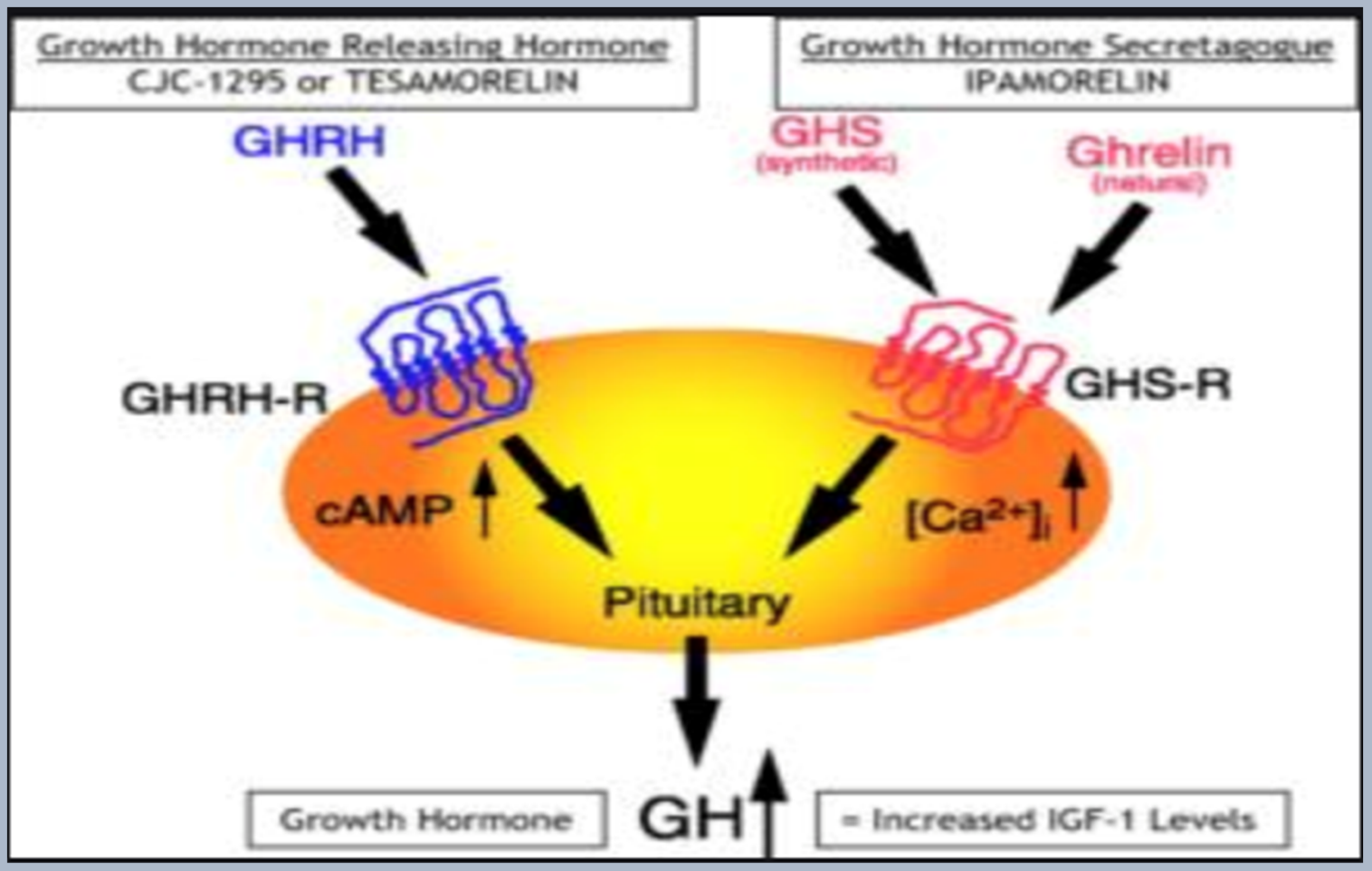
Teichman SL, et al. Prolonged stimulation of growth hormone (GH) an insulin-like growth factor-1 secretion by CJC 1295, a long-acting analog of GH-releasing hormone, in healthy adults. J Clin Endocrinol Metab. 2006;91(3):799-805.

CJC-1295/Ipamorelin Uses

- Ipamorelin = 3rd generation GHRP
- Selective agonist of ghrelin/Growth hormone secretagogue receptor
- Ddoes not raise hormones of concern including cortisol, prolactin or ghrelin
- CJC-1295 = GHRH amplifier
- Ipamorelin = GHRP inducer
- Combo improves strength of GH pulse and increases # of GH secreting cells (somatotrophs)
- Frequently used in ergogenic and weight management protocols – used concurrently improves results
- Improved energy levels

Raun K, et al. Ipamorelin, the first selective growth hormone secretagogue. Eur J Endocrinol. 1998;139(5):552-61.

Ipamorelin + CJC-1295



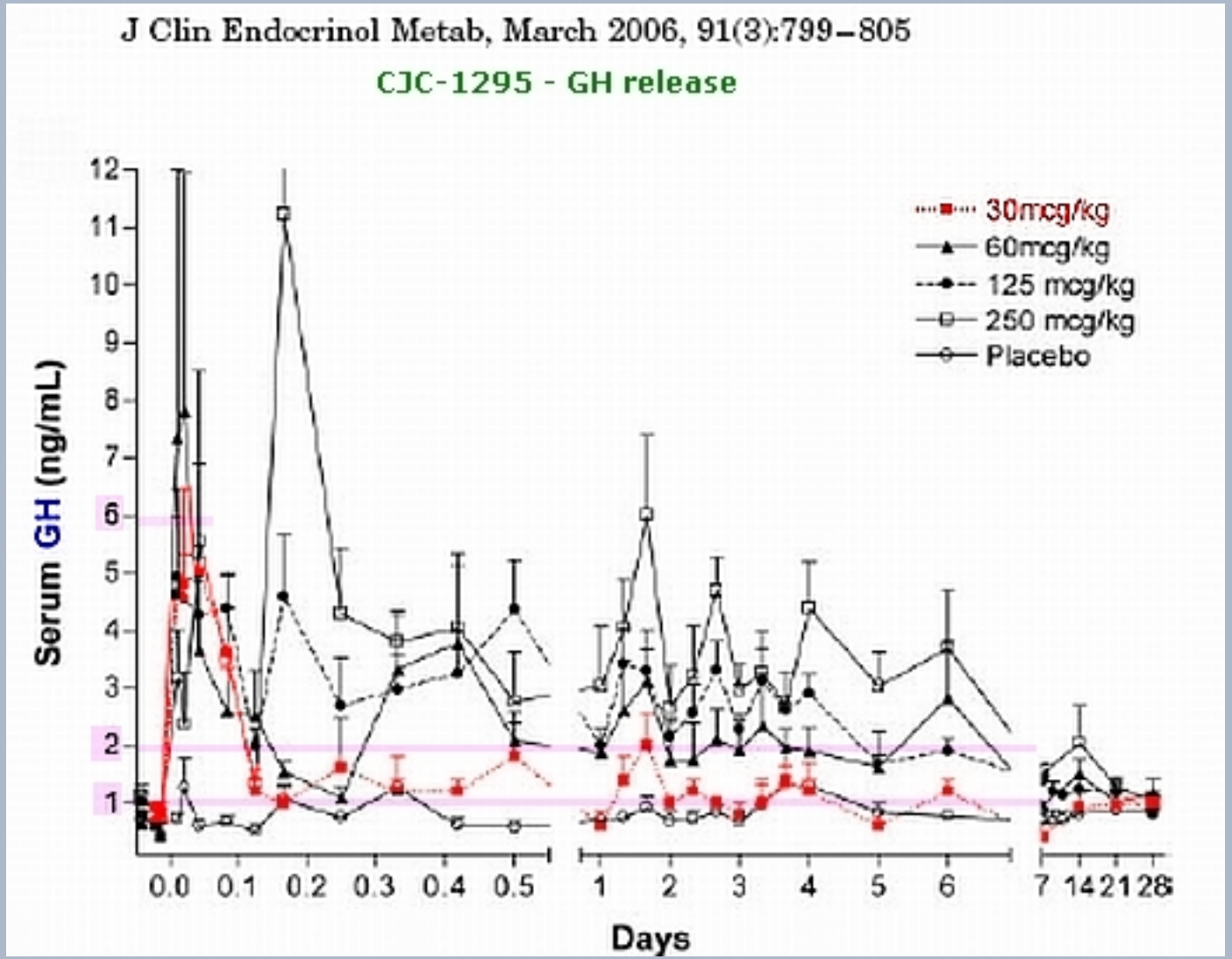
Raun K, et al. Ipamorelin, the first selective growth hormone secretagogue. Eur J Endocrinol. 1998;139(5):552-61.

CJC-1295 Clinical Study

- 2006 study injecting 30-250mcg/kg
- 24 healthy adults
- IGF-1 levels increased w/in 8 hours post injection
- No adverse events or S.E.'s

Teichman S, et al. The journal of clinical Endocrinology and Metabolism. 2006;91(3):799-805.

CJC-1295 GH Release

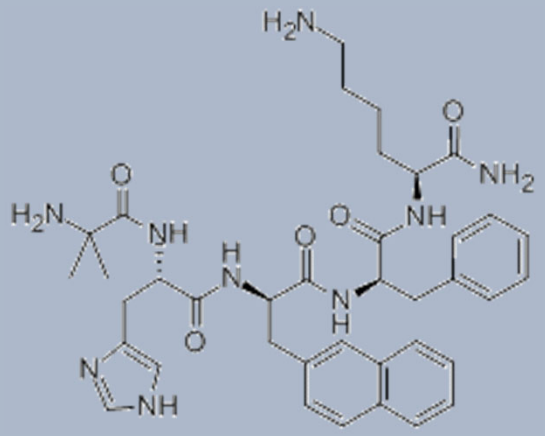


CJC-1295

- Reported to promote REM and slow wave sleep
  - Independent of age
- Helps stimulate highest level of muscle growth and memory retention
- Inhibits cortisol release

Perras B, et al. Sleep and endocrine changes after intranasal administration of growth-hormone releasing hormone in young and aged humans. Psychoneuroendocrinology. 1999;24(7):743-57.

Ipamorelin



- Growth releasing hormone
- Alternative to GHRP-2 or GHRP-6
- No spikes in cortisol or prolactin at lower dosages
- Increases LBM
- Lowers body fat
- Anti-aging
- Supports improved sleep, memory
- Lower side effects
- Used in conjunction w/ CJC-1295

CJC-1295 + Ipamorelin Dosing

- CJC-1295 w/o DAC + Ipamorelin dosing =
  - Supplied as 1mg/1mg per ml (1mg CJC1295 + 1mg Ipamorelin per ml), 2mg/2mg per ml and 2mg/1mg per ml
  - Dosage = 0.05 ml to 0.1 ml QHS, 5 days out of the week.
  - It is best to dose on an empty stomach, at least 2-3 hours after the last meal of the day.
- In comparative data, CJC 1295 reported to be more effective at than Sermorelin
- Sermorelin's binding time to GHRH receptors was reported to be 8-12 minutes
- CJC 1295's binding time > 30 minutes
- CJC+ DAC dosing = 600mcg weekly

Walker RF. Sermorelin: a better approach to management of adult-onset growth hormone insufficiency? Clin Interv Aging. 2006;1(4):307-8.

CJC-1295 + Ipamorelin Dosing

- GH may be mitogenic
- If patient prone to cancer or has cancer, use with caution
- GH may mask symptoms of hypothyroidism
- Make sure to test thyroid hormone levels (Free and Total T3, T4, TSH and thyroid antibodies)

PT-141 (Bremelanotide)

- Melanocortin receptor agonist – stimulates alpha melanocyte stimulating hormone (α-MSH)
- Highest affinity for MCR-4 (melanocortin receptor-4)
- MC4R stimulation contributes to improved sexual function in both men (improving penile erections) and women (increasing desire and arousal)
- Sexual stimulation SE discovered while creating Melanotan II, synthetic peptide used for tanning
- Unlike PDE5 inhibitors, PT-141 interacts with CNS and elicits a more desirous sexual response

Rosen RC, et al. Evaluation of the safety, pharmacokinetics and pharmacodynamic effects of subcutaneously administered PT-141, a melanocortin receptor agonist, in healthy male subjects and in patients with an inadequate response to Viagra. Int J Impotence Res. 2004;16:315-42.

PT-141 Dosage

- Supplied as PT-141 for injection, 10mg/ml 2ml vial
- Dose = 2mg (0.2ml) starting dose, 45 minutes - 1 hour before sex
- Recommended to inject 1mg (0.1ml) for test dose, then add 1mg (0.1ml) more 30 minutes later
- Titration may be needed to achieve desired response
- Duration of effects after administration is 24-72 hours
- Dose 2 x weekly initially, then may increase if tolerated

Clayton AH, Lucas J, DeRogatis LR, et al. Phase 1 randomized placebo-controlled, double blind study of the safety and tolerability of bremelanotide coadministered with ethanol in healthy male and female participants. Clin Ther. 2017;39(3):514-526.

King SH, Mayorov AV, Balse-Srinivasan P, et al. Melanocortin receptors, melanotropic peptides and penile erection. Curr Top Med Chem. 2007;7(11):1098-1106.

PT-141 = FDA Approved Vyleesi ™

- 2019 FDA approved intranasal PT-141 = Vyleesi™ - Palatin Technologies in Paramus NJ
- Approved as PRN treatment for premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD)
- Off label uses for male sexual dysfunction
- Use cautiously if taking PDE5 inhibitors – ↑ risk of priapism in men
- Side effects encountered in clinical studies (over 600 patients) were mild to moderate nausea, flushing and/or headache

Clayton AH, Althof SE, Kingsberg S, et al. Bremelanotide for female sexual dysfunctions in premenopausal women: a randomized, placebo-controlled dose-finding trial. Women's Health. 2-16;12(3):325-337.

Vyleesi ™ Cautions/Warnings

- Using before bedtime may affect sleep patterns
- Contraindicated in patients who have uncontrolled hypertension or known cardiovascular disease
- Discontinue use if priapism develops in men (an erection lasting longer than 4 hours).
  - It is **NOT** recommended to use PT-141 injection concurrently with any PDE5 inhibitor in men due to risk of priapism.
- May slow gastric emptying and impact absorption of concomitantly administered oral medications.

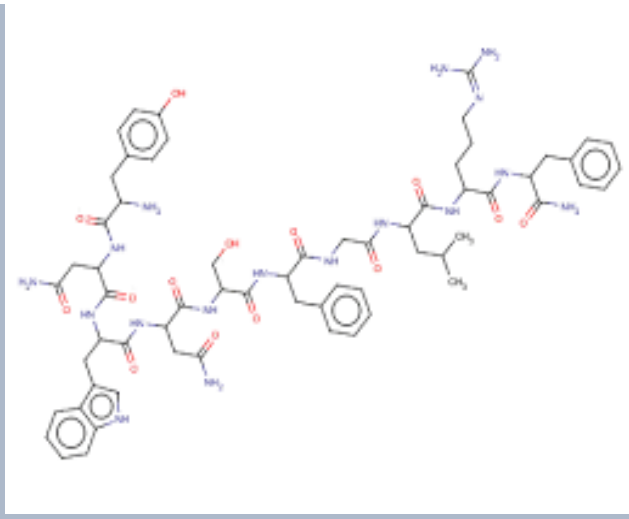
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210557s000lbl.pdf

Vyleesi ™ Cautions/Warnings

- Reported to significantly decrease the systemic exposure of orally administered naltrexone - avoid use with orally administered naltrexone containing products intended to treat alcohol or opioid addiction. (Vyleesi FDA approved monograph)
- Hyperpigmentation may occur, including face, gums (gingiva) and breasts.
  - Risk increases in those with darker skin color.
  - May be an irreversible process
- Although the concurrent use of PT-141 and alcohol should be discouraged, a Phase 1 study (n=24 -12 men, 12 women) using SubQ bremelanotide (PT-141) and ethanol concurrently reported no synergistic side effects while using both

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210557s000lbl.pdf

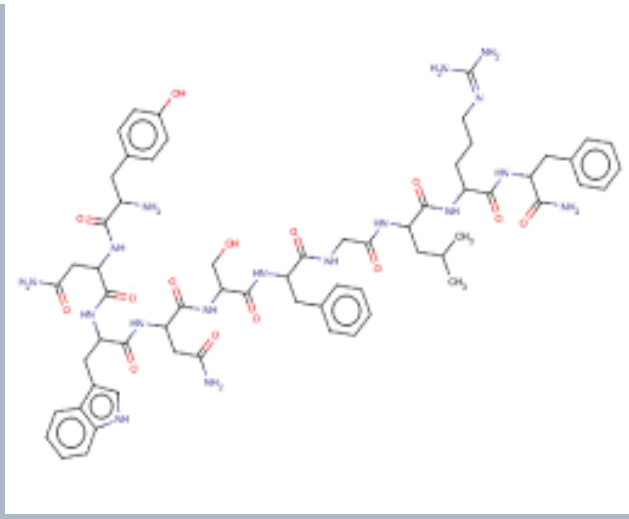
Kisspeptin



- Endogenous 54 amino acid
- 1st discovered in 1996 as metastasis inhibitor in melanoma cell lines
- Derived from KISS1 gene
- Important in hypothalamic regulatory circuits involved in reproductive homeostasis – hypothalamic-pituitary-gonadal axis
- Directly stimulates gonadotropin-releasing hormone release via G protein-coupled receptor 54

Grachev P, et al. Stress regulation of kisspeptin in the modulation of reproductive function. Adv Exp Med Biol. 2013;784:431-54.

Kisspeptin – Gonadal Axis



- Critical role in onset of puberty
- Regulates seasonal reproduction
- Regulates gonadal steroidal feedback to hypothalamus
- Has direct gonadal effects
- Can stimulate secretion of aldosterone and the release of insulin.
- Has effects on the limbic system

- de Roux N, et al. Hypogonadotropic hypogonadism due to loss of function of the KiSS1-derived peptide receptor GPR54. Proc Natl Acad Sci U S A. 2003;100:10972–10976.
- Revel FG, et al. Kisspeptin: a key link to seasonal breeding. Rev Endocr Metab Disord. 2007;8:57–65.

Kisspeptin – Gonadal Axis

- 2005 clinical study reported kisspeptin infusion increased plasma gonadotropin and testosterone levels

  Dhillo WS, et al. Kisspeptin-54 stimulates the hypothalamic-pituitary gonadal axis in human males. J Clin Endocrinol Metab. 2005;90:6609–6615.

- 2013 human clinical study reported that continuous kisspeptin infusion restored pulsatile LH secretion in humans with NKB or NK3R inactivating mutations that lead to infertility
- Suggests that NKB acts through kisspeptin to modulate downstream effects on GnRH secretion.
- Kisspeptin may be novel agent for infertility

Young J, et al. Kisspeptin restores pulsatile LH secretion in patients with neurokinin B signaling deficiencies: physiological, pathophysiological and therapeutic implications. Neuroendocrinology. 2013;97:193–202.

Kisspeptin – Gonadal Axis

- Stress is reported to inhibit reproductive function by suppressing GnRH release

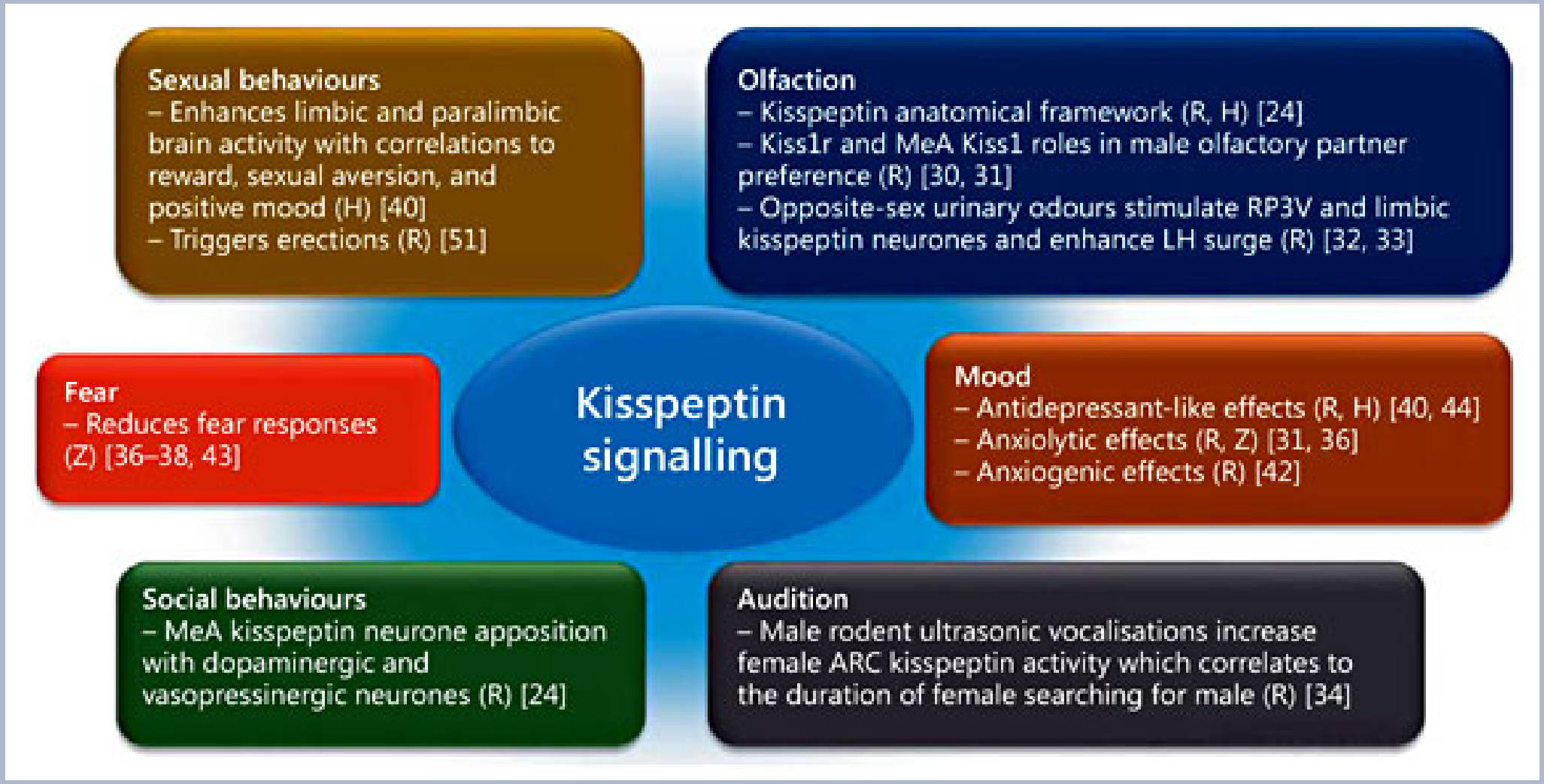
- Reduced Kisspeptin expression reported lower in :
  - Stress
  - Restraint
  - Insulin-induced hypoglycemia
  - Lipopolysaccharide (LPS)

Cates PS, et al. The influence of 17beta-oestradiol on corticotrophin-releasing hormone induced suppression of luteinising hormone pulses and the role of CRH in hypoglycaemic stress-induced suppression of pulsatile LH secretion in the female rat. Stress. 2004;7:113–118.

Kisspeptin – Gonadal Axis

- A 2017 human study in 29 healthy heterosexual males
- IV kisspeptin (1 nmol/kg/h) or placebo over 75 min
- Reported increases in circulating kisspeptin and enhanced limbic brain activity
- Specifically in response to sexual and couple-bonding stimuli
- Kisspeptin's enhancement of limbic brain structures correlate with psychometric measures of:
  - Reward
  - Drive
  - Mood
  - Sexual desire

Comninos AN, et al. Kisspeptin modulates sexual and emotional brain processing in humans. J Clin Invest. 2017;127(2):709-19.



Comninos AN, et al. J Clin Invest. 2017;127(2):709-19.

Kisspeptin Indications/Uses

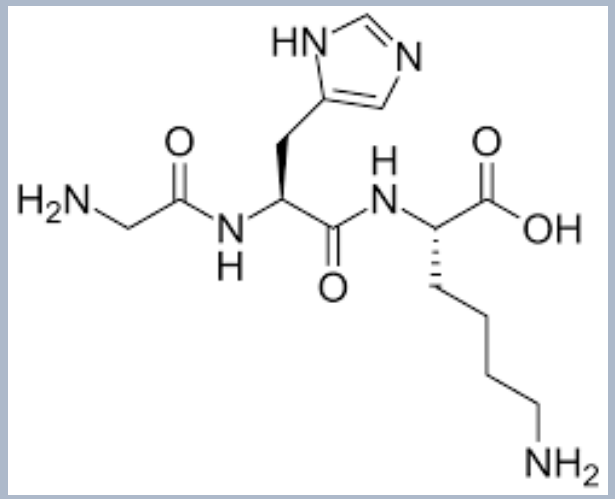
- Primary hypogonadism
- Endogenous testosterone support
- Fertility support
  - Improving ovulation and egg implantation
  - Preventing Ectopic Pregnancy
- Physiologic Hormone Replacement Therapy (HRT)
- Physiologic Gonadotropin Hormone Release
- Diabetes/insulin resistance support
- Potential Adjunct of Metastatic Prevention in Cancer

Clarke H, et al. Comprehensive review on kisspeptin and its role in reproductive disorders. Endocrinol Metab. 2015;30:124-41.

Kisspeptin Dosage

- Supplied: 1mg/ml 3ml vial
- Dosage = 0.1 ml (100 mcg) SQ daily at bedtime
- Use at bedtime is not required

GHK-Cu



- GHK (glycyl-L-histidyl-L-lysine) + Cu (Copper peptide)
- GHK Isolated in 1973
- Complexed with Copper
  - Important in antioxidant defense
  - Tissue formation
- Improves wound healing and tissue regeneration
  - Increases collagen, elastin, glycosaminoglycans
  - Increases angiogenesis
  - Anti-inflammatory
  - Increases stem cells

Kang YA, et al. Copper-GHK increases integrin expression and p63 positivity by keratinocytes. Arch. Dermatol. Res. 2009;301:301–306.

Arul V, et al. Biotinylated GHK peptide incorporated collagenous matrix: A novel biomaterial for dermal wound healing in rats. J. Biomed. Mater. Res. B Appl. Biomater. 2005;73:383–391.

GHK-Cu

- Anti-aging support
  - Skin regenerative
  - Protective
  - Decreases skin thinning
  - Improves skin elasticity and firmness
  - UV protection

- Estrogen deficiency following menopause results in atrophic skin changes and ↑ skin aging

- Wound healing/ tissue repair
  - Promotes survival of epidermal basal stem cells

Leyden J, et al. Skin care benefits of copper peptide containing facial cream," in Proceedings of the American Academy of Dermatology Meeting, New York, NY, USA, February 2002.
Pickert L,. et al. The effect of the human peptide GHK on gene expression relevant to nervous system function and cognitive decline. Brain Sci. 2017;7(2):pii:E20.

GHK-Cu

Also

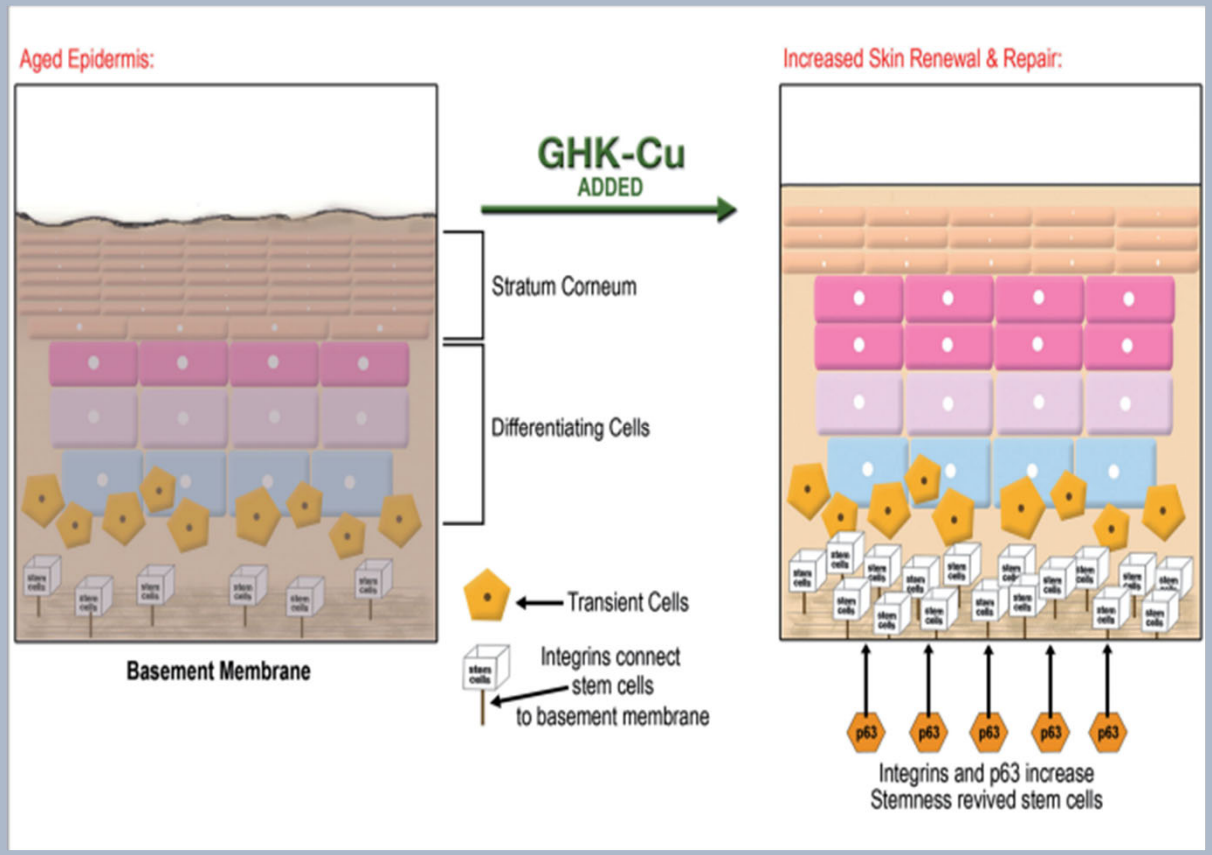
- Hair growth/re-growth
- Antioxidant/Anti-inflammatory
- Neuroprotection
  - Cognitive / neurodegeneration support

- GHK declines with age
  - a study reports that at age 20, plasma level GHK = approx. 200 ng/mL (10^{-7} M) and by age 60, levels drop to approximately 80 ng/mL

Hostynek J, et al. Human skin retention and penetration of a copper tripeptide in vitro as function of skin layer towards anti-inflammatory therapy. Inflam Res. 2010;59(11):983–88.

Carraway JH. 2004. Using Aldara, copper peptide, and niacinamide for skin care. Aesthet Surg J 24:83–84.

GHK-Cu



Pickart L, et al. SDFW J. 2010;136(6):1-9.

GHK-Cu

Dosages:

- Facial Cream 0.5% 15gm
  - Apply to area(s) 2-3 times daily
  - Use a small test area of skin on initial therapy to determine sensitivity
- Scalp foam 0.5% 50ml
  - Rub into scalp 2 times daily
  - Use a small test area of skin on initial therapy to determine sensitivity
- SubQ injection
  - 1-2mg daily for 10-21 days
  - IM or SubQ

Hostynek J, et al. Human skin retention and penetration of a copper tripeptide in vitro as function of skin layer towards anti-inflammatory therapy. Inflam Res. 2010;59(11):983–88.

Carraway JH. 2004. Using Aldara, copper peptide, and niacinamide for skin care. Aesthet Surg J 24:83–84.

GHK-Cu

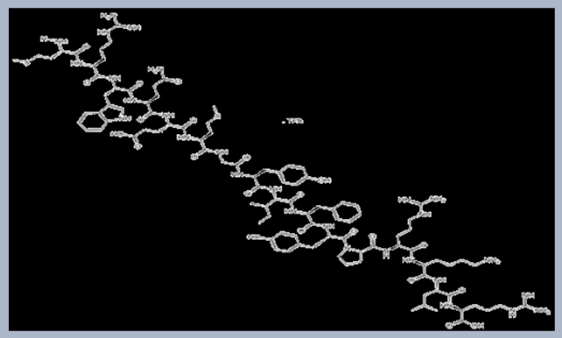
- Monitor patient for copper toxicity
  - Luna of nail turns blue
  - Corrects over 4-6 weeks after discontinuation
  - Recommend zinc chelate, 30mg daily for potential zinc/copper imbalance
  - A quality multiple vitamin/mineral with zinc chelate is also a good recommendation

- Topical use may result in irritation, redness and/or itching - discontinue use if topical dermatitis develops.

Hostynek J, et al. Human skin retention and penetration of a copper tripeptide in vitro as function of skin layer towards anti-inflammatory therapy. Inflam Res. 2010;59(11):983–88.

Carraway JH. 2004. Using Aldara, copper peptide, and niacinamide for skin care. Aesthet Surg J 24:83–84.

MOTS-c



- Mitochondrial-derived protein (MDP)
- Preserves mitochondrial function and cell viability under stress
- Key role in cellular stress response
- TARGETS =
  - Metaflammation
  - Metabolic signaling issues
  - Anti-aging

Cohen P. Mitochondrial-derived peptides: novel hormones that regulate metabolism during aging. Innovation Aging. 2018;2(1):333-34.

MOTS-c

- Increases intracellular NAD^+ levels
- Effects mediated by SIRT1
- MOTS-c levels decline with age
- Improves insulin sensitivity

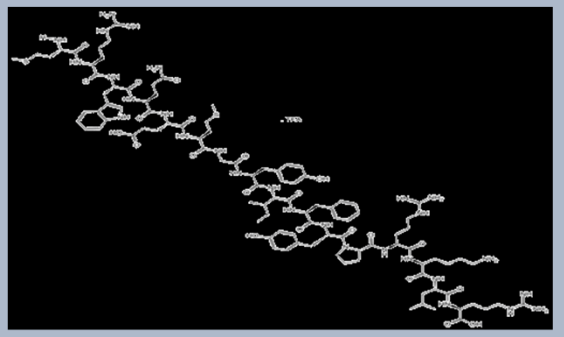
Cohen P. Mitochondrial-derived peptides: novel hormones that regulate metabolism during aging. Innovation Aging. 2018;2(1):333-34.

MOTS-c

- Increases glucose utilization and fatty acid oxidation
- Decreases oxidative phosphorylation
- Increases endogenous AICAR levels
- AMPK activation
- Increases glucose update into muscle cells
- Upregulates thermogenic gene expression
- Upregulates brown adipose tissues (BAT)
- Reported to increase adipose thermogenic activation to promote cold adaptation

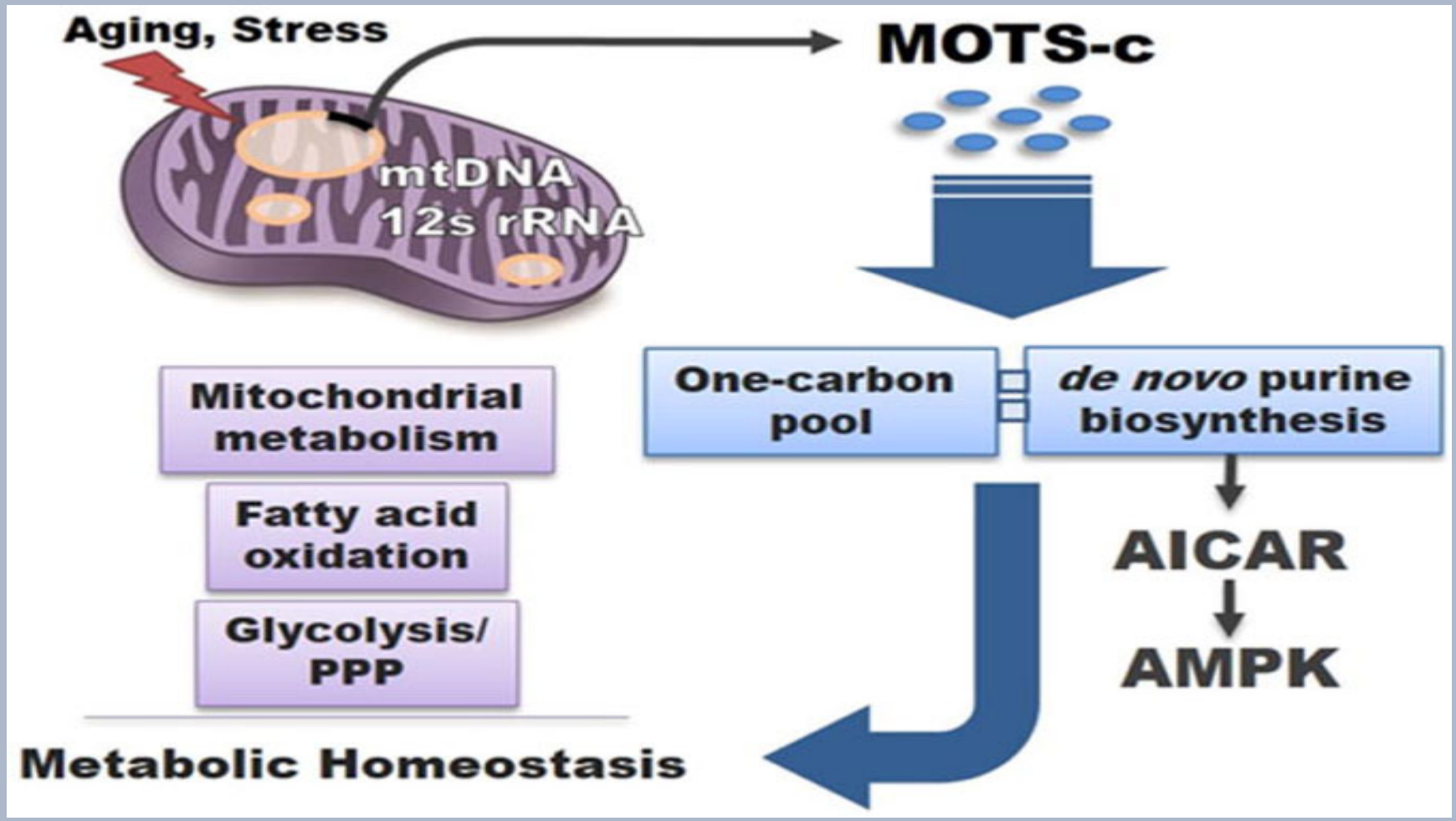
Lee C, et al. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. Cell Metab. 2015; 21:443–54.

MOTS-c Uses



- Metaflammatory conditions
- Obesity and weight gain
- Type 2 diabetes / Insulin Resistance
- Anti-aging
- Cytoprotective
- Mitochondrial dysfunction

Lee C, et al. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. Cell Metab. 2015; 21:443–54.



Lee C, et al. Cell Metab. 2015;21(3):443–454.

MOTS-c Dosage

- 10mg SQ three times a week for 4 weeks, then 10mg SQ weekly
- Reported safe in recommended dosages
- As with all injections, redness and pain at the site of injection may be present.
- MOTS-c targets folate cycle and de novo purine biosynthesis pathways
- Possible a depletion of intracellular 5-methyl tetrahydrofolate (5-MTHF) may occur when using MOTS-c protocols.
- Recommended check homocysteine and folate levels in patients taking MOTS-c
- Folinic acid or 5-MTHF, up to 1,200 mcg daily, between injections in the protocol, especially in those prone to folate deficiencies

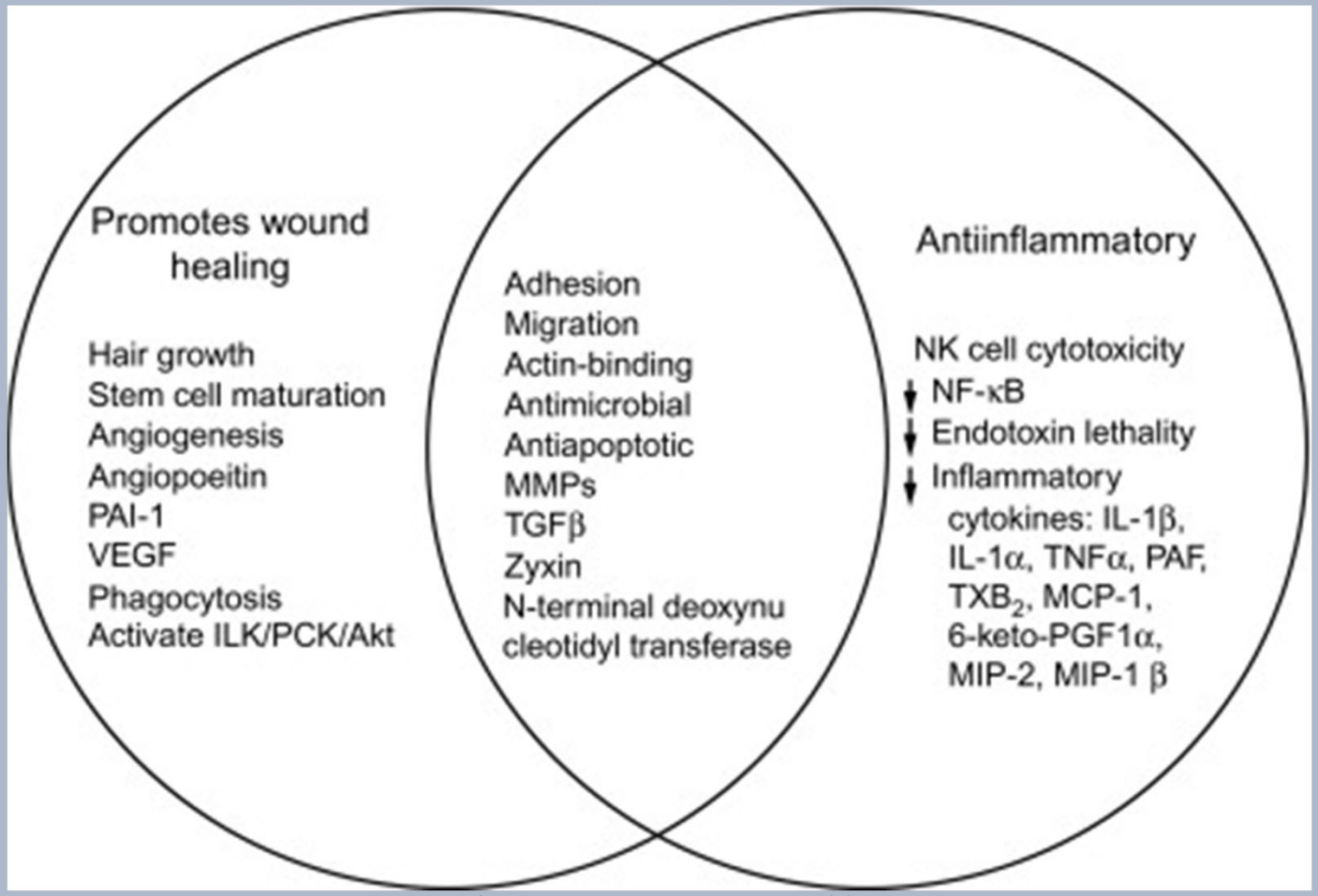
Lee C, et al. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. Cell Metab. 2015; 21:443–54.

ABP-7

- Antibacterial peptide 7 aka TB-500
- Fragment of Thymosin beta-4
- Supports immunity
  - Antimicrobial
  - Improves T cells
  - Use with Thymosin alpha 1
  - Helps modulate human GUT mucosal immune system
- Nephroprotective
- Helps decrease scar tissue formation
  - Reduces level of myofibroblasts
- Neuroprotective

Elltsur Y, et al Thymosin alpha 1 and thymosin beta 4 modulate human colonic lamina propria lymphocyte function. Immunopharmacology. 1990;20(2):89-96.
Reti R, Kwon E, Qui P, et al. Thymosin B4 is cytoprotective in human gingival fibroblasts. Eur J Oral Sci. 2008;116(5):424-30.
Popoli PR, Pepponi A, Martire et al. Neuroprotective Effects of Thymosin B4 in Experimental Models of Excitotoxicity. Ann. N.Y. Acad. Sci.2007;1112: 219–224.

ABP-7 Summary



Reti R, Kwon E, Qui P, et al. Thymosin B4 is cytoprotective in human gingival fibroblasts. Eur J Oral Sci. 2008;116(5):424-30.
Popoli PR, Pepponi A, Martire et al. Neuroprotective Effects of Thymosin B4 in Experimental Models of Excitotoxicity. Ann. N.Y. Acad. Sci.2007;1112: 219–224.

ABP-7 Applications

- Immune support
- Soft Tissue Repair – tendon, ligament, muscle
  - Sports/athletic injuries
- Kidney support
- Pressure or venous stasis ulcers
- Conditions requiring immune response modulation
- Brain issues if autoimmunity suspected
- Ischemic stroke

Kleinman HK, Sosne G. Thymosin B4 promotes dermal healing. Vitam Horm. 2016;102:251-75.

Yarmola EG, Kilmenko ES, Fujita G, et al. Thymosin beta4: actin regulation and more. Ann NY Acad Sci. 2007;1112:76-85.

ABP-7 Dosage

- General dosage (supplied 3mg/ml)
  - 300 mcg – 1 gram daily, SubQ
  - Depending upon clinical presentation
  - Do not dose for more than 3 months
  - Cycle if needed long-term – 3 months on, 1 month off
- Can use with BPC-157 concurrently
- Individual dosage requirements may vary based on clinical presentation
- ABP-7 banned by WADA

Adrenomedullin

- 52 amino acid vasodilatory peptide discovered 1993
- Structurally related to calcitonin gene-related peptide (CGRP) – target CGRP receptors
- Normally present in adrenal medulla, heart, lung and kidney, plasma and urine
- Exogenous Uses:
  - Antioxidant
  - Cardiovascular support – improved cardiac output and overall survival in CHF
  - Renal support

Hinson JP, et al. Adrenomedullin, a multifunctional regulatory peptide. Endocrine Rev. 2000;21(2):138-67.

Adrenomedullin

- 2000 randomized, double-blind placebo controlled study
- N= 7 CHF patients and 7 normal
- Adrenomedullin (AM) administration decreased mean arterial pressure, increased HR and increased cardiac index
- Increased urinary volume and sodium excretion
- IV infusion of AM has beneficial hemodynamic and renal effects in patietns w/ CHF

Nagaya N, et al. Hemodynamic, renal, and hormonal effects of adrenomedullin infusion in patients with congestive heart failure. Circulation. 2000;101(5):498-503.

Adrenomedullin

- May increase plasma prolactin
- IV Infusion :
  - Human adrenomedullin (19.9 pmol/kg/min) in 250ml 0.9%NS as IV infusion over 20 minutes
- Common reported adverse events in IV administration were facial flushing, heat sensation, and palpitations.

Meeran K, et al. **Circulating adrenomedullin does not regulate systemic blood pressure but increases plasma prolactin after intravenous infusion in humans: a pharmacokinetic study**. J Clin Endocrinolog Metab. 1997;82(1):95-100.

Peptides - BPC-157

- BPC-157 – Body Protection Compound
- Gastric Pentadecapeptide – 15 Amino Acids
- Gly-Glu-Pro-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val
- Derived from human gastric juice
- GUT IMMUNE BRAIN axis
- Cytoprotective
- Anti-inflammatory
- Supports GUT mucosal lining
- Protects and heals inflamed GUT mucosa

Sikiric P, et al. Brain-gut axis and pentadecapeptide BPC 157: Theoretical and practical implications. Curr Neuropharmacol. 2016;14:857-65.
Seiwerth S, et al. BPC157 and blood vessels. Curr Pharm Des. 2014;20(7):1121-5.

BPC-157

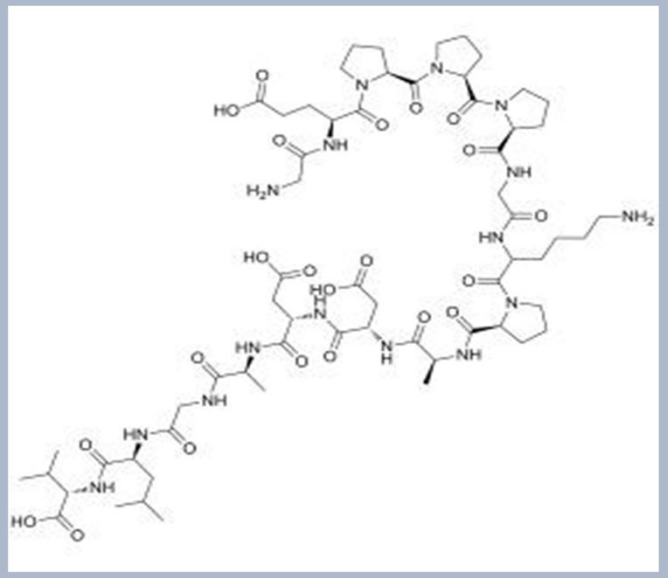
- Effective in decreasing metainflammatory signaling
- Downregulates TNF-alpha
- Improves cell survival under oxidative stress conditions
- Decreases neuroinflammation

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

Seiwerth S, et al. BPC157 and blood vessels. Curr Pharm Des. 2014;20(7):1121-5.

BPC-157 Patient Benefits

- Accelerated wound healing
- Decreases inflammation
- Increased fibroblast
- Nitric oxide improvement
- Improves digestive function
- Enhanced vascular expression of VEGFR2



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

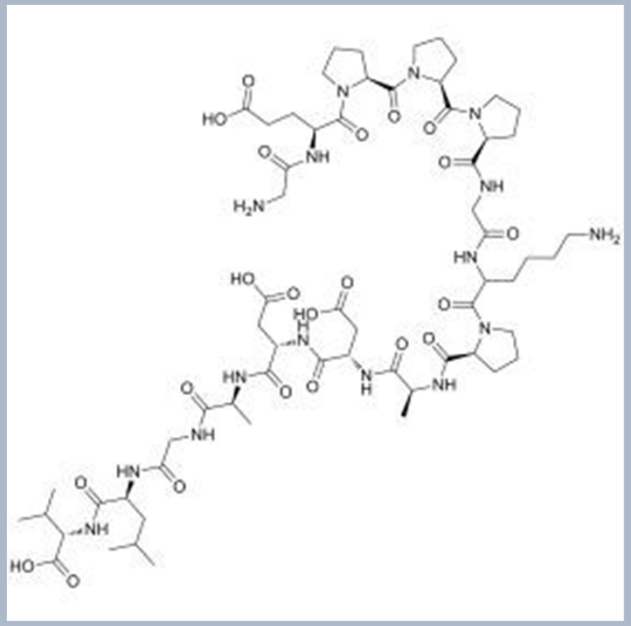
Seiwerth S, et al. BPC157 and blood vessels. Curr Pharm Des. 2014;20(7):1121-5.

BPC-157

- Potent angiomodulatory factor
- Improves tissue regeneration
  - Granulation
  - Fibroblast recruitment
  - Collagen formation
- Upregulates growth hormone

Sikiric P, et al. Brain-gut axis and pentadecapeptide BPC 157: Theoretical and practical implications. Curr Neuropharmacol. 2016;14:857-65.
Seiwerth S, et al. BPC157 and blood vessels. Curr Pharm Des. 2014;20(7):1121-5.

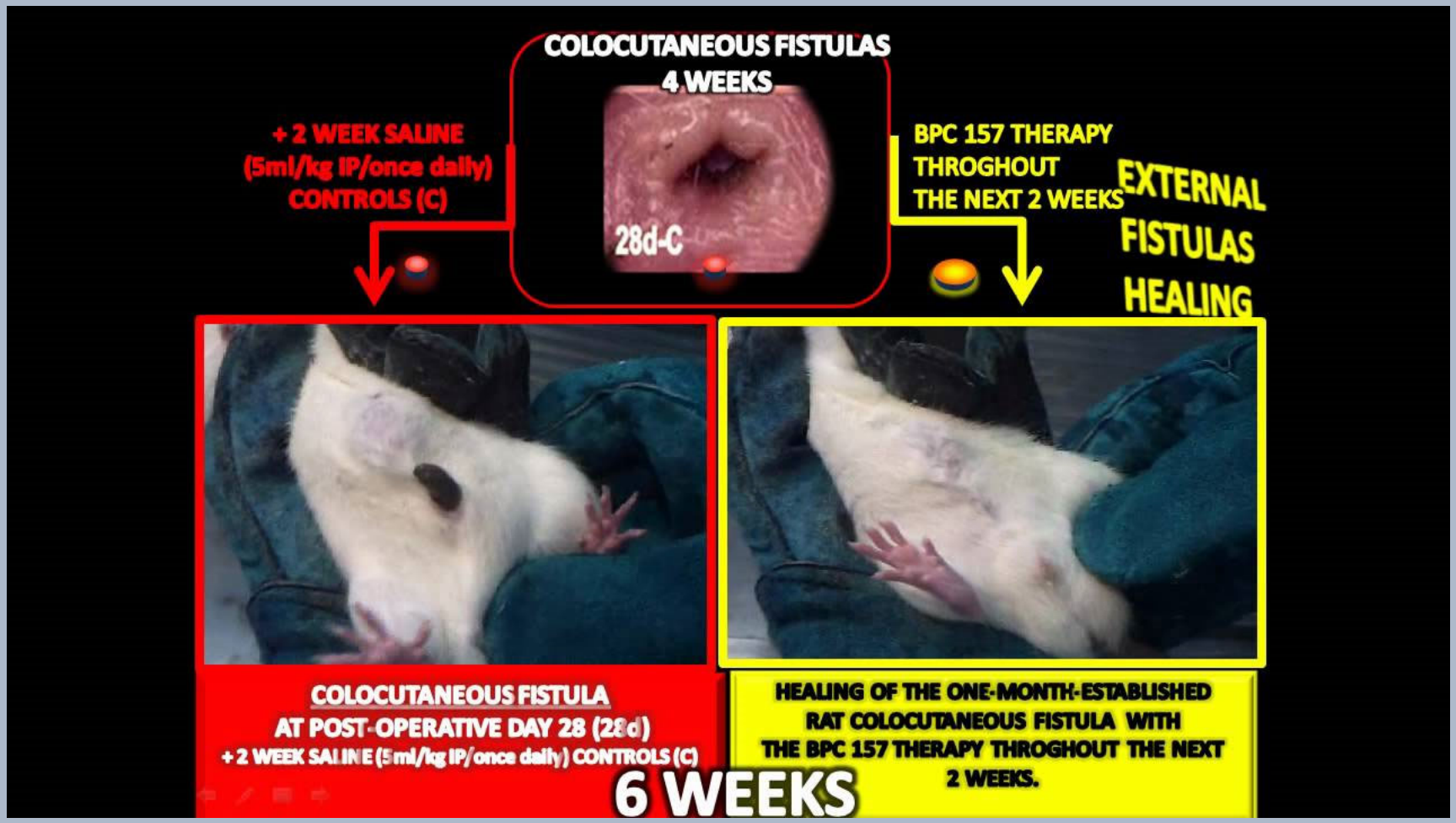
BPC 157 - GUT



- Gastric protection
  - Antiulcer peptidergic agent
  - Cytoprotective
  - Nitric Oxide (NO) improvement
    - BPC 157 interacts with nitric oxide (NO) system, both NOS-substrate (L-arginine) and NOS-blocker (L-NAME), including the regulation of a blood pressure
  - Helps improve GI mucosal integrity
  - Ulcerative colitis in lab studies
  - Decreases NSAID and alcohol gastric side effects

Sikiric P, et al. Focus on ulcerative colitis: stable gastric pentadecapeptide BPC 157. Curr Med Chem. 2012;19(1):126-32.

BPC 157 and Colovesical Fistulas – 2016 RAT study



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

BPC-157

- INJECTION - Prescribing is often based on body weight using 2mcg/kg to as much as 10mcg/kg twice daily
- Commonly used doses range from 200mcg - 400mcg twice daily (400mcg to 800mcg daily)
- If used twice daily, intramuscular injection as close to the injury as possible or via subcutaneously for systemic purposes
- Use for 2-4 weeks before discontinuing; cease therapy for 2weeks, then restart therapy if needed

- BPC-157 is angio**modulatory** – however, use with caution in conditions where angiogenesis may be a problem (tumors)

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

Seiwerth S, et al. BPC157 and blood vessels. Curr Pharm Des. 2014;20(7):1121-5.