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Peptides To Avoid In Cancer

Current state and development of peptides in cancer treatment

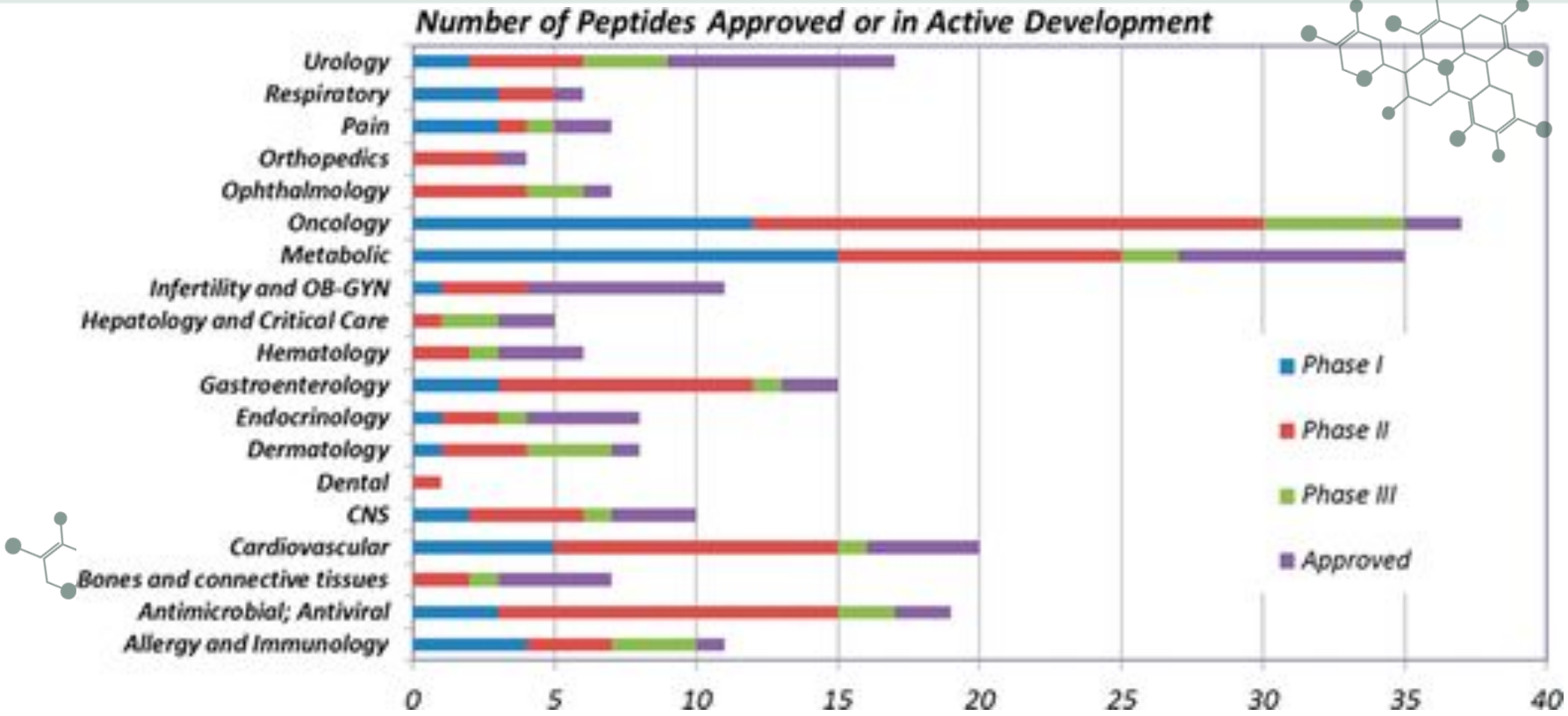
- Cancer is a leading cause of death in the industrialized world

- Current treatments are losing efficacy due to:
  - Drug resistance
  - Lack of tumor selectivity
  - Solubility
  - Cost

- Peptides are promising therapy for cancer due to
  - Ease of synthesis
  - High target specificity and selectivity
  - Low toxicity

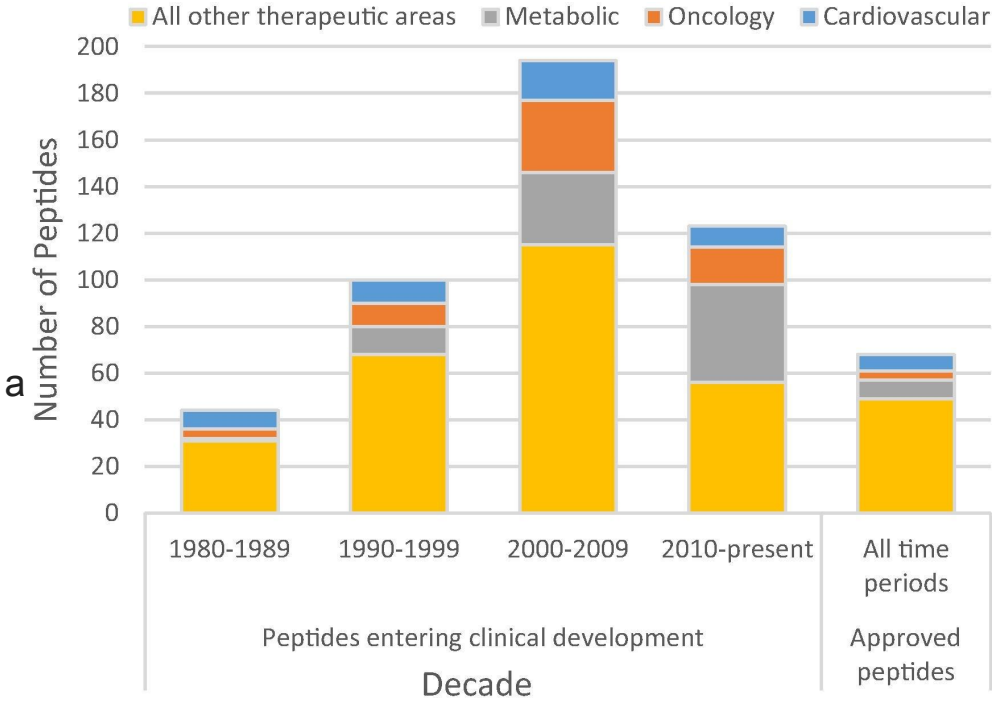
Susan Marqus, Elena Pirogova and Terrence J. Evaluation of the use of therapeutic peptides for cancer treatment. Journal of Biomedical Science201724:21. 21 March 2017

Peptides In Development



Peptide Development: Areas of Interest

What Peptides are being Developed?



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Peptides in Cancer: The Strategies

Peptides: can be utilized in a number of different ways in treating Cancer:

- Peptides directly as drugs (e.g., as angiogenesis inhibitors)
- Tumor targeting agents that carry cytotoxic drugs and radionuclides (targ
  chemotherapy and radiation therapy)
- Hormones
- Vaccines
- potential diagnostic tool and biomarkers

Out of these different possibilities, peptide drugs currently available in the market
come from peptide hormone therapy and tumor targeting agents carrying radionuclides (peptide receptor radio nuclide therapy and imaging).

Exceptions to these are two short chain peptide-related drugs, bortezomib mifamurtide. There is a tremendous progress in other areas such as peptide-vaccine development and peptide angiogenesis inhibitors, and sev clinical trials are underway which is expected to bear fruit in near future providing better options to millions of cancer patients.

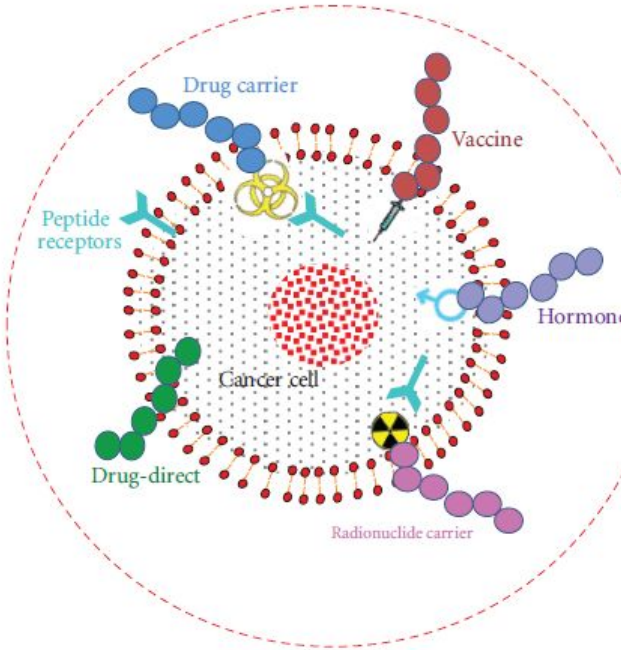

FIGURE 1: Different possible treatment options of cancer peptides. Peptides can be used as anticancer drug, cytotoxic carrier, vaccine, hormones, and radionuclide carrier.

Susan Marqus, Elena Pirogova and Terrence J. Evaluation of the use of therapeutic peptides for cancer treatment. Journal of Biomedical Science201724:21. 21 March 2017

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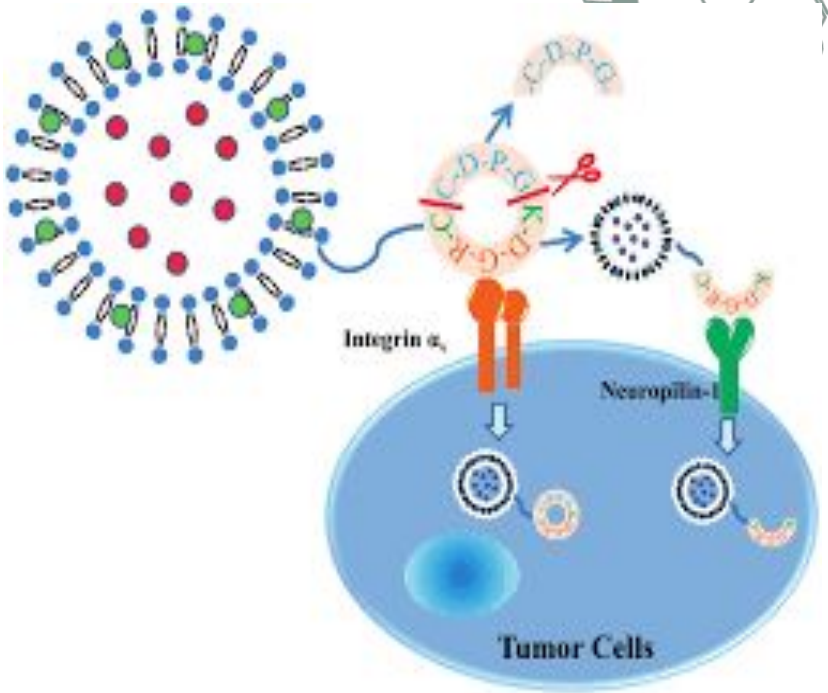
Current state and development of peptides in cancer treatment

- More Common Peptide Drugs
  - PNC27
  - SSRB1
  - iRGD
  - Thymosin Alpha-1
  - Antimicrobial peptides
  - Cell penetrating peptides
  - Met Enkephalin



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Peptides Which Should be Viewed with Caution

- LL-37
- Thymosin Beta-4
- GH Secretagogues

- Dihexa?
- GH Secretagogues?

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LL-37: Natural Cathelicidin

AMPs (antimicrobial peptides) represent the first line of defense against invading pathogens.

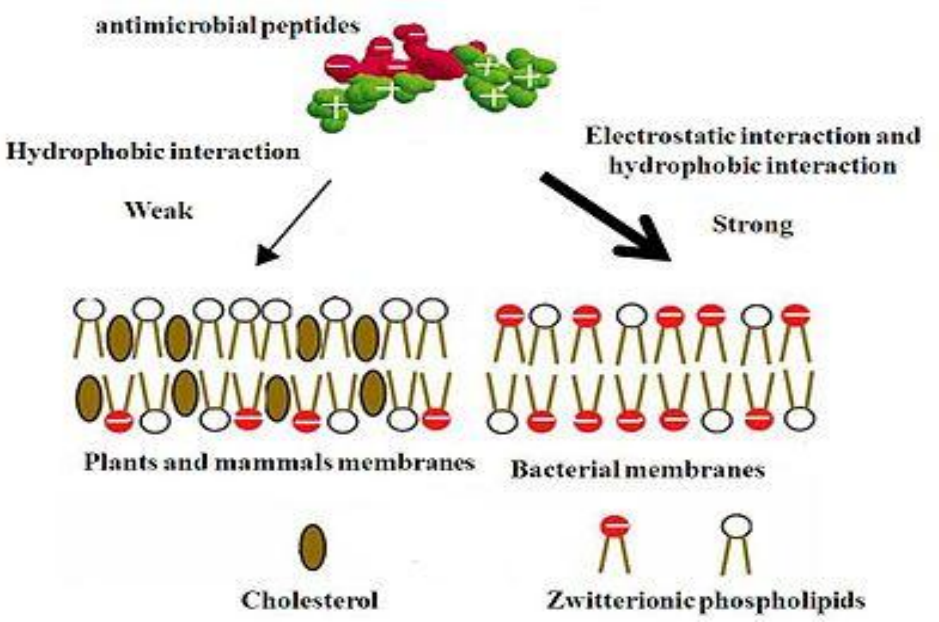
Cathelicidin family of AMPs have been identified in various mammalian species, and LL-37 is the only known human cathelicidin, cleaved from CAP18 (a cationic antimicrobial polypeptide of 18-kDa).

In addition to its broad spectrum of bactericidal activities, LL-37 has a wide range of inflammatory/immune modulatory actions. It also fights viruses and fungi as well.

Found mainly expressed in the intestines.

Cancer properties addressed by peptides: Cationic Cell Membranes

- Negatively charged cancer cells
  - Targeted directly by Anti-Microbial Peptides (AMPs)



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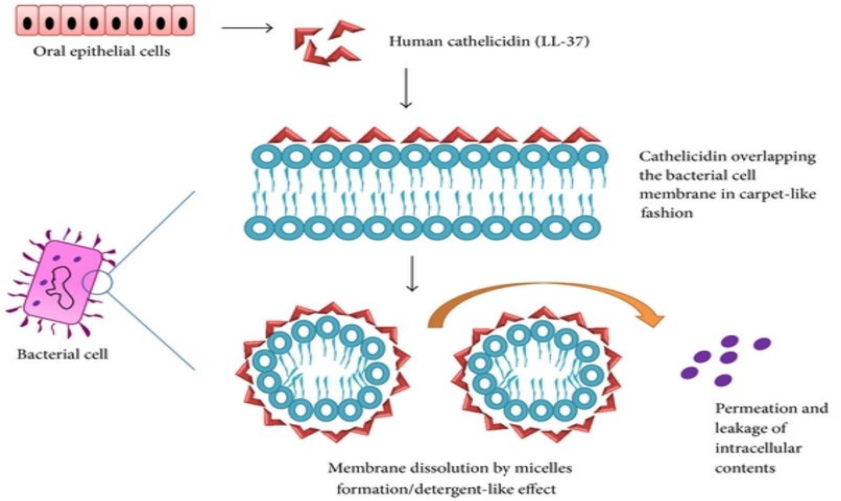
Phospholipid Targeting: AMPs

- Big area of research

- Pore Membrane Peptides Mechanism of Action:
  - Toroidal pore formation
    - A loose bundle of peptides modulates the membrane into a lipid headgroup-lined pore
  - Formation of a pore with a barrel-stave conformation
    - A tight bundle of amphiphilic peptides forms a hydrophilic pore across the membrane
  - The carpet mode
    - peptides remain on the surface of the membrane until a threshold is reached to facilitate a breakdown in membrane integrity



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LL-37: Uses In Cancer

Cell Physiol Biochem. 2018;47(3):1060-1073. doi: 10.1159/000490183. Epub 2018 May 25.

Roles and Mechanisms of Human Cathelicidin LL-37 in Cancer.

Chen X[1,2], Zou X[1], Qi G[2,3], Tang Y[1], Guo Y[1], Si J[1,2], Liang L[4].

Author information

Abstract

LL-37, the C-terminal peptide of human cathelicidin antimicrobial peptide (CAMP, hCAP18), reportedly increases resistance to microbial invasion and exerts important physiological functions in chemotaxis, promotion of wound closure, and angiogenesis. Accumulating evidence indicates that LL-37 also plays a significant role in human cancer. LL-37 induces tumorigenic effects in cancers of the ovary, lung, breast, prostate, pancreas, as well as in malignant melanoma and skin squamous cell carcinoma. In contrast, LL-37 displays an anti-cancer effect in colon cancer, gastric cancer, hematologic malignancy and oral squamous cell carcinoma. Mechanistically, LL-37-induced activation of membrane receptors and subsequent signaling pathways lead to alteration of cellular functions. Different membrane receptors on various cancer cells appear to be responsible for the tissue-specific effects of LL-37. Meanwhile, the findings that vitamin D-dependent induction of cathelicidin in human macrophages activates the anti-cancer activity of tumor-associated macrophages (TAMs) and enhances antibody-dependent cellular cytotoxicity (ADCC) support critical roles of vitamin D-dependent induction of cathelicidin in cancer progression. This review describes novel advances involving the roles and mechanisms of human cathelicidin LL-37 in cancer.

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LL-37: Uses In Cancer

- It has been proposed that the cell and tissue effects induced by LL-37 are mainly mediated via activation of specific cell surface receptors, membrane channels or intracellular targets that are differentially expressed in different cell types.

- These LL-37-targeted receptors include at least four G protein-coupled receptors (GPCRs), three receptor tyrosine kinases (RTKs), a ligand-gated ion channel (LGIC) and toll-like receptors (TLRs)

- Vitamin D-dependent can induce cathelicidin production in human macrophages for the anti-cancer activity of tumor-associated macrophages (TAMs) and enhances antibody-dependent cellular cytotoxicity (ADCC) support critical roles of vitamin D-dependent induction of cathelicidin in cancer progression.

Thymosin Beta-4

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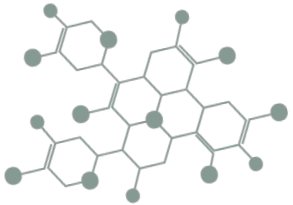
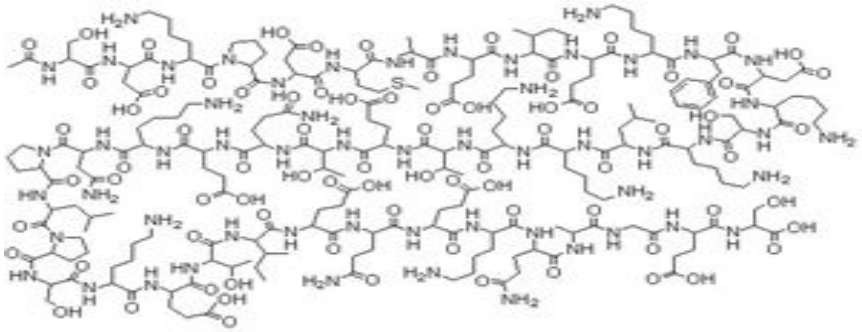
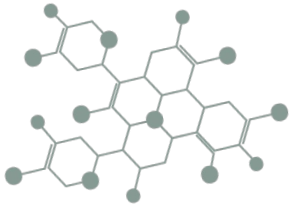
Thymosin Beta-4

- Thymosin β-4 (TB4 or TB-500)
  - Originally isolated from calf thymus
- 43 aa sequence encoded by gene TMSBX4
- Present in all human cells; naturally found in higher concentrations in tissue damaged area
- Frequent in sports doping for the past 20 years for its ability to decrease injury times and reduce delayed onset muscle soreness.







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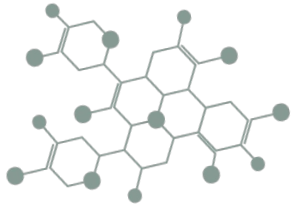
Thymosin Beta-4



- Tβ4 is an actin monomer-sequestering protein.
- Ubiquitous and naturally-occurring protein in wound bed.
- Role in tissue repair: Tβ4 gene first to be upregulated upon injury
- Stimulates wound healing by enhanced angiogenesis, cell migration, promotes stem cell differentiation
- Anti-inflammatory properties: decrease inflammatory cytokines
- Currently in Phase 3 clinical trials.

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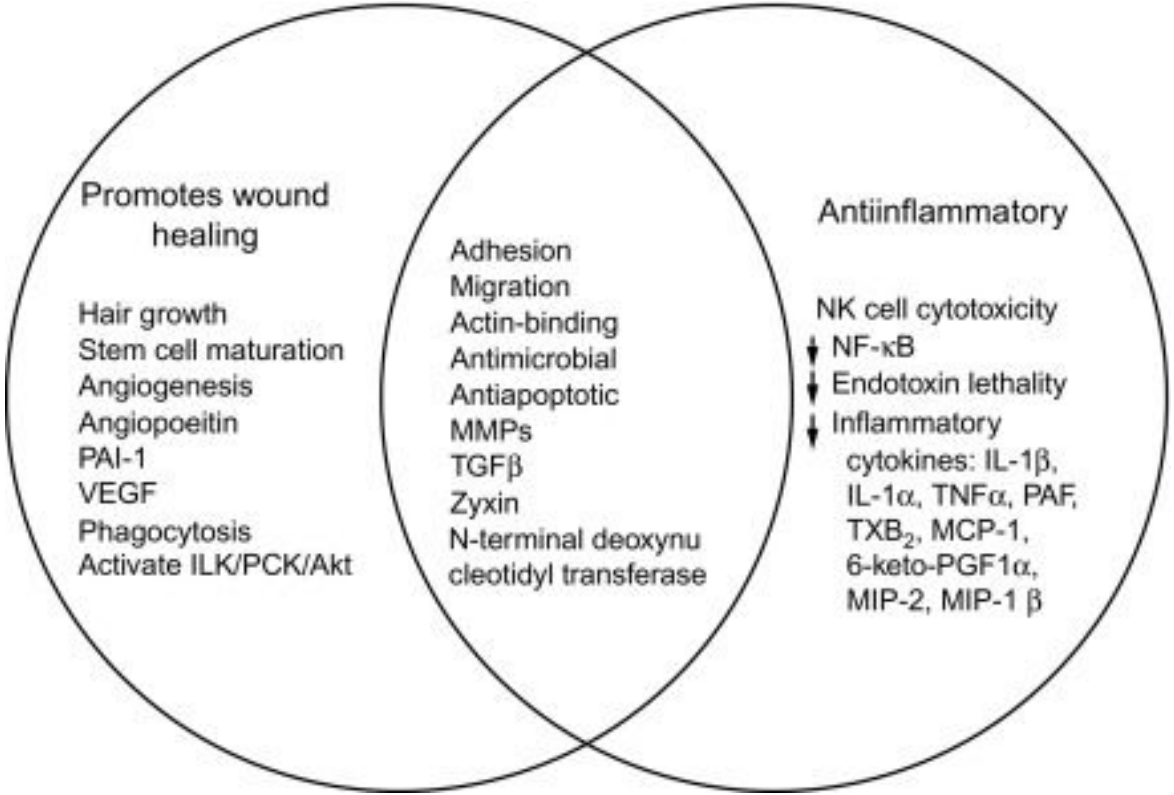
Thymosin Beta-4: Mechanisms



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Thymosin Beta-4: Mechanisms

Actin Sequestering Protein

TB4 up-regulates cell building proteins such as **actin**, a protein along with **myosin**, forms the contractile filaments of muscle cells and create the cytoskeleton for healing.

Up-regulation of actin allows promotes healing, cell growth, cell migration and cell proliferation

Improves cell migration to site of injury (IL-8 and MMP2 attract stem cells to area of injury

The FASEB Journal • Research Communication

Regenerative protein thymosin β-4 is a novel regulator of purinergic signaling

Kevin W. Freeman,*,[1] Brian R. Bowman,[†] and Bruce R. Zetter*,[2]

*Vascular Biology Program and Department of Surgery, Children's Hospital, Boston, and Harvard Medical School, Boston Massachusetts, USA; and [†]Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts, USA

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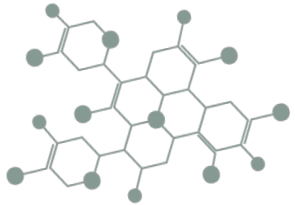
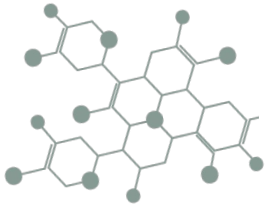
Thymosin Beta-4: Mechanisms

- Also encourages genetic changes to help with antioxidant and anti-inflammatory effects.





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PLoS one

Thymosin Beta 4 Prevents Oxidative Stress by Targeting Antioxidant and Anti-Apoptotic Genes in Cardiac Fibroblasts

Sandeep Kumar, Sudhiranjan Gupta*

Division of Molecular Cardiology, Department of Molecular Medicine, College of Medicine, Texas A&M Health Science Center, Scott & White, Central Texas Veterans Health Care System, Temple, Texas, United States of America

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Thymosin Beta-4: Mechanisms

- Increased levels of extracellular ATP via ATP synthase and subsequent activation of P2X4 purigenic receptor to promote cell migration[79]
- Found to promote mesenchymal stem cell proliferation via IL-8-depedent mechanism[75]

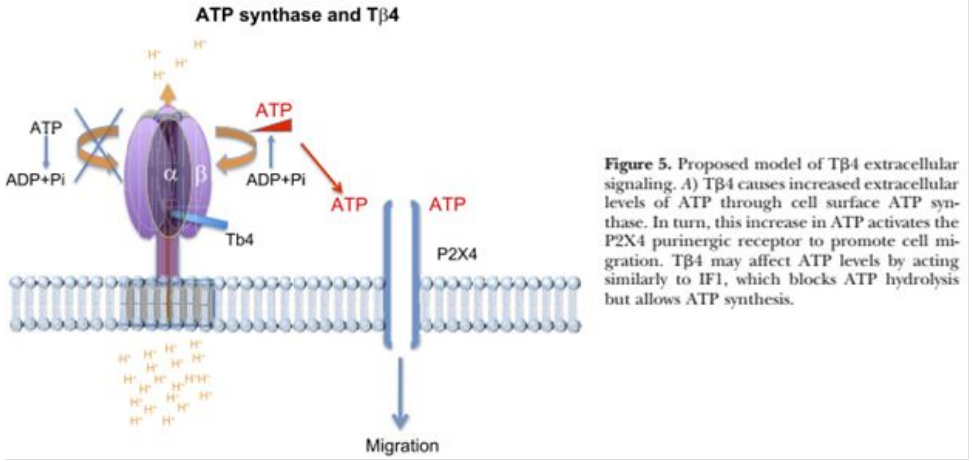

Figure 5. Proposed model of Tβ4 extracellular signaling. *A*) Tβ4 causes increased extracellular levels of ATP through cell surface ATP synthase. In turn, this increase in ATP activates the P2X4 purinergic receptor to promote cell migration. Tβ4 may affect ATP levels by acting similarly to IF1, which blocks ATP hydrolysis but allows ATP synthesis.

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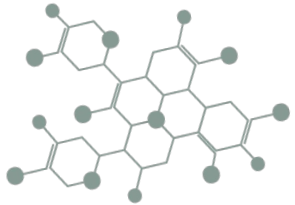
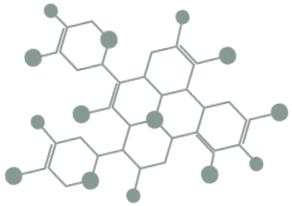
Thymosin Beta-4: Uses



- Athletic recovery: preventing DOMS
- Post surgery/injury
- Hair loss
- Cardiac healing
- TBI
- Lung Inflammation
- Corneal Healing



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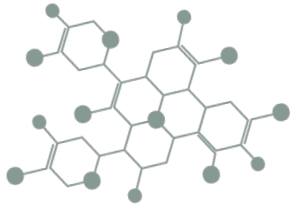
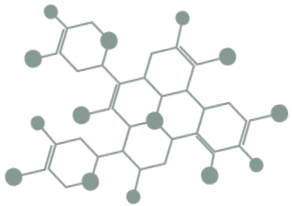
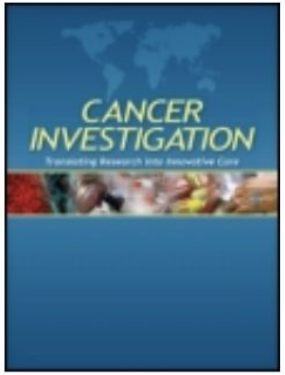
Thymosin Beta-4: Dose



- General dosing:
  - 750 mcg (.25ml) daily, SubQ
  - Depending upon clinical presentation
  - Do not dose for more than 3 months
  - Cycle if needed
- TB4 use with other healing peptides concurrently
- Individual dosage requirements may vary based on clinical presentation





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Cancer Investigation

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Roles and Mechanisms of β-Thymosins in Cell Migration and Cancer Metastasis: An Update

Sirinapa Sribenja, Sopit Wongkham, Chaisiri Wongkham, Qizhi Yao & Changyi Chen

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TAILOR MADE COMPOUNDING

Thymosin Beta-4: Cancer Studies

Pathology – Research and Practice 213 (2017) 1139–1143

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Original article

Thymosin beta-4 overexpression correlates with high-risk groups in gastric gastrointestinal stromal tumors: A retrospective analysis by immunohistochemistry

Sevinç Şahin[a,*], Ozgur Ekinci[b], Selda Seçkin[a], Ayse Dursun[b]

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Gastric gastrointestinal stromal tumor
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ABSTRACT

Background: Thymosin beta-4 (Tβ4) is a protein that is linked to a number of important biological actions and recently tumor progression and poor prognosis of some tumors. The aim of this study was to evaluate Tβ4 expression in gastric GISTs and correlate with some clinicopathological characteristics related with prognosis and clinical outcome in order to add further data to the current literature.
Methods: Tβ4 antibody was applied to the 4 μm-thick paraffin sections of 57 gastric GISTs by immunohistochemistry.
Results: Tβ4 expression was found to be directly correlated with higher risk groups, tumor size, mitotic count, cellularity, and necrosis while it was inversely correlated with overall survival (OS) by univariate analysis ($p = 0.000$, $p = 0.001$, $p = 0.000$, $p = 0.025$, $p = 0.023$, and $p = 0.042$, respectively). The direct association between Tβ4 expression and risk groups were also supported by multivariate analysis ($p = 0.000$, $\beta = 0.497$, $t = 4.374$).
Conclusion: Overexpression of Tβ4 was found to be related with predictive characteristics for tumor progression and adverse prognosis. Thus, we suggest that overexpression of Tβ4 might play a role in the progression of gastric GISTs and might be used as a potential prognostic tool as well as a target for novel therapies.

ABBS

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doi: 10.1093/abbs/gmw070
Advance Access Publication Date: 12 August 2016
Original Article

OXFORD

Original Article

Thymosin beta 4 silencing suppresses proliferation and invasion of non-small cell lung cancer cells by repressing Notch1 activation

Dayu Huang[1], Shaohua Wang[2], An Wang[1], Xiaofeng Chen[2,*], and Huijun Zhang[2,*]

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Abstract

Thymosin beta 4 (Tβ4), a pleiotropic actin-sequestering polypeptide that is involved in wound healing and developmental processes, has been reported to be strongly associated with tumorigenesis. A recent tissue microarray analysis showed that Tβ4 was highly expressed in certain tumor cells, including lung cancer. However, the exact expression pattern and the role of Tβ4 in non-small cell lung cancer (NSCLC) have not to our knowledge been investigated. In the present study, we confirmed that Tβ4 expression was increased in NSCLC tissues and cell lines. *Tjl4* gene silencing in A549 and H1299 cells inhibited cell proliferation, migration, and invasion *in vitro* and decreased tumor growth *in vivo*. Mechanistic investigations revealed a significant decrease in Notch1 activation in *Tjl4* gene-silenced cells. Moreover, restoring the Notch1 expression attenuated the function of *Tjl4* silencing in NSCLC cells. Taken together, these findings suggest that Tβ4 may play an oncogenic role in NSCLC progression and may be a novel molecular target for anti-NSCLC therapy.

SCIENTIFIC REPORTS

OPEN

Global Proteomics-based Identification and Validation of Thymosin Beta-4 X-Linked as a Prognostic Marker for Head and Neck Squamous Cell Carcinoma

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pted: 26 July 2017
ished online: 22 August 2017

Li-Hsing Chi[1,2,3], Wei-Min Chang[2], Yu-Chan Chang[2], Yung-Chieh Chan[2], Chia-Chen Tai[2], Kam-Wing Leung[4,5], Chi-Long Chen[4,7], Alexander TH Wu[1], Tsung-Ching Lai[2], Yu-Chuan (Jack) Li[1,8] & Michael Hsiao[1,2,9]

Head and neck squamous cell carcinoma (HNSCC) represents a major health concern worldwide. We applied the matrix-assisted laser desorption/ionization (MALDI) imaging mass spectrometry (IMS) to analyze paired normal (N) and tumor (T) samples from head and neck squamous cell carcinoma as well as liquid chromatography with tandem mass spectrometry (LC-MS/MS) analysis in HNSCC cell lines to identify tumor-associated biomarkers. Our results showed a number of proteins found to be over-expressed in HNSCC. We identified thymosin beta-4 X-linked (TMSB4X) is one of the most significant candidate biomarkers. Higher TMSB4X expression in the tumor was found by N/T-paired HNSCC samples at both RNA and protein level. Overexpression of TMSB4X was found significantly associated with poor prognosis of overall survival (OS, $P = 0.006$) and recurrence-free survival (RFS, $P = 0.013$) in HNSCC patients. Silencing of TMSB4X expression in HNSCC cell line reduced the proliferation and invasion ability *in vitro*, as well as inhibited the cervical lymph node metastasis *in vivo*. Altogether, our global proteomics analysis identified that TMSB4X is a newly discovered biomarker in HNSCC whose

Thymosin beta 4 and thymosin beta 10 expression in hepatocellular carcinoma

W. Theunissen,[1,2] D. Fanni,[2] S. Nemolato,[2] E. Di Felice,[2] T. Cabras,[3] C. Gerosa,[2] P. Van Eyken,[4] I. Messana,[3] M. Castagnola,[5] G. Faa[2]

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[2]Department of Surgical Sciences, Division of Pathology, University Hospital San Giovanni di Dio, University of Cagliari, Italy
[3]Department of Life and Environmental Sciences, University of Cagliari, Italy
[4]Department of Pathology, K.U. Leuven, Belgium
[5]Institute of Biochemistry and Clinical Biochemistry, Faculty of Medicine, Catholic University, Rome, Italy

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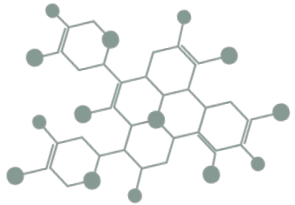
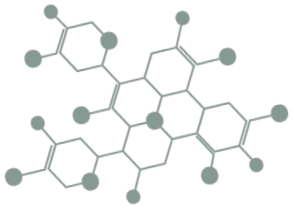
Thymosin Beta-4: Cancer Studies



Endogenous upregulation through genetic changes have correlated β-thymosins with cell migration and metastatic potential of human cancers such as melanoma, thyroid carcinoma, colon cancer, and prostate cancer.

This has only been seen in cellular studies.



TAILOR MADE COMPOUNDING

Thymosin Beta-4: Cancer Studies

Thymosin Beta-4 Is Elevated in Women With Heart Failure With Preserved Ejection Fraction

Chester L. Drum, MD, PhD; Warren K. Y. Tan, BSc; Siew-Pang Chan, PhD; Leroy S. Pakkiri, PhD; Jenny P. C. Chong, BSc; Oi-Wah Liew, PhD; Tze-Pin Ng, MBBS; Lieng-Hsi Ling, MBBS, MD; David Sim, MBBS; Kui-Toh G. Leong, MBBS; Daniel P. S. Yeo, MBBS; Hean-Yee Ong, MBBCh; Fazlur Jaufeerally, MBBCh; Raymond C. C. Wong, MBBS; Ping Chai, MBBS; Adrian F. Low, MBBS; Pia Davidsson, PhD; Mathias Liljeblad, PhD; Ann-Sofi Söderling, PhD; Li-Ming Gan, MD, PhD; Ratan V. Bhat, PhD; Kristy Purnamawati, PhD; Carolyn S. P. Lam, MBBS, PhD; A. Mark Richards, MBChB, MD, PhD, DSc

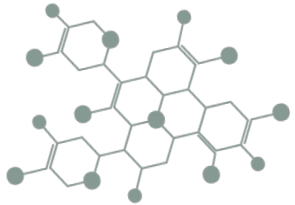
Background—Thymosin beta-4 (TB4) is an X-linked gene product with cardioprotective properties. Little is known about plasma concentration of TB4 in heart failure (HF), and its relationship with other cardiovascular biomarkers. We sought to evaluate circulating TB4 in HF patients with preserved (HFpEF) or reduced (HFrEF) ejection fraction compared to non-HF controls.

Table 1. Demographics and Clinical Characteristics of Cohort

	Controls (n=219)	HFpEF (n=219)	HFrEF (n=219)	*P*-Value
Clinical characteristics				
Age, y	65.0±9.0	68.2±11.2	64.7±11.2	0.001
Sex				
Male	106 (48.4%)	104 (47.5%)	117 (53.4%)	0.409
Female	113 (51.6%)	115 (52.5%)	102 (46.6%)	
Ethnicity				
Chinese	148 (67.6%)	141 (64.4%)	148 (67.6%)	0.656
Malay	51 (23.3%)	56 (25.6%)	50 (22.8%)	
Indian	20 (9.1%)	19 (8.7%)	20 (9.1%)	
Other	0 (0.0%)	3 (1.4%)	1 (0.5%)	
BMI, kg/m^2	25.0±3.9	27.6±5.7	25.5±5.4	<0.001
Heart rate, beats/min	66.8±9.4	71.8±13.4	76.4±14.0	<0.001
Systolic BP, mm Hg	138.4±20.1	132.1±20.6	124.3±22.2	<0.001
Diastolic BP, mm Hg	76.1±10.8	69.3±11.4	70.1±11.9	<0.001
NYHA Class				
I	210 (95.9%)	51 (24.9%)	46 (21.5%)	<0.001
II	9 (4.1%)	124 (60.5%)	129 (60.3%)	
III & IV	0 (0.0%)	30 (14.6%)	39 (18.2%)	
Ischemic etiology	…	87 (39.7%)	145 (66.2%)	<0.001
Coronary artery disease	…	68 (34.2%)	120 (57.4%)	<0.001
Hypertension	91 (41.7%)	177 (85.9%)	155 (71.4%)	<0.001
Diabetes mellitus	27 (12.4%)	121 (58.5%)	131 (60.1%)	<0.001
Atrial fibrillation/flutter	3 (1.4%)	64 (30.8%)	50 (23.2%)	<0.001
Peripheral vascular disease	0 (0.0%)	3 (1.5%)	10 (4.6%)	0.002
Cancer	7 (3.3%)	5 (2.5%)	11 (5.1%)	0.330

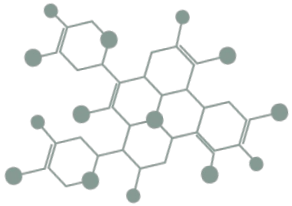
TAILOR MADE COMPOUNDING

Thymosin Beta-4: Cancer Studies



Yes, the phase 1a and 1b review said the following:
"The reported potential of T4 to influence the metastatic potential of certain malignancies through its ability to promote angiogenesis and stimulate cell migration warranted close follow-up for any potential cancers.4,5 No cancers were identified during a 6-month follow-up period."

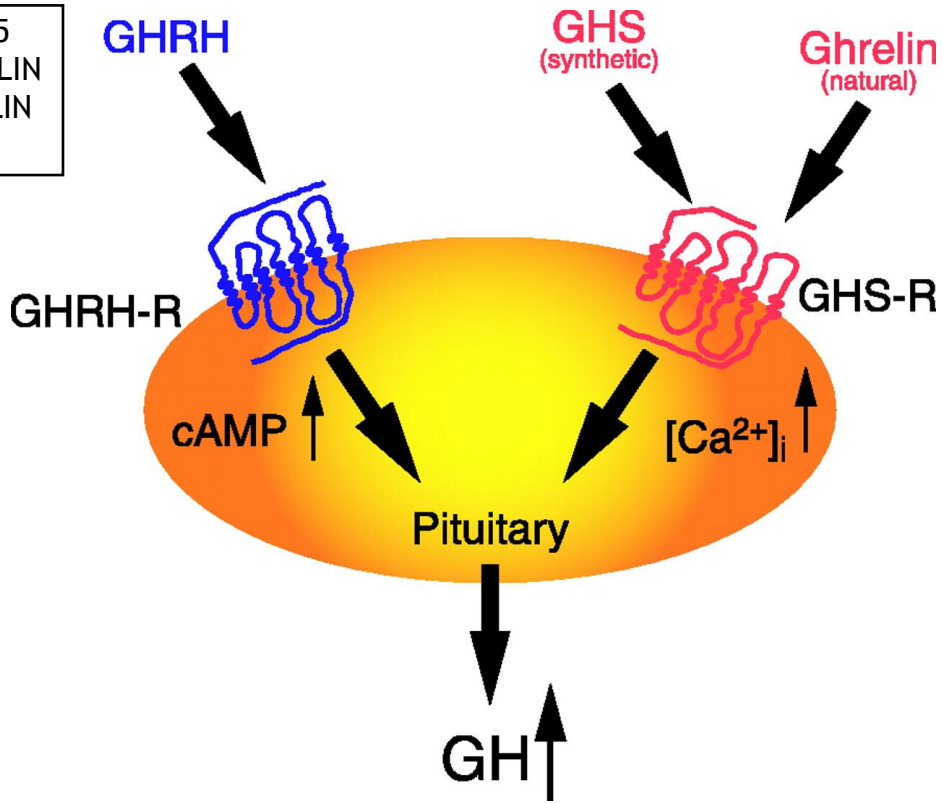
The dose used in clinical trials for MI were 1.2g IV. The other clinical dosage recommendations are .06%of this dose.



TAILOR MADE COMPOUNDING

Growth Hormone Optimization Protocol:

CJC-1295
TESAMORELIN
SERMORELIN
GRF-18



IPAMORELIN
HEXARELIN
GHRP6
GHRP2
MK-677

TAILOR MADE COMPOUNDING

Protection of IGF-1 BP3?

Articles

Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis

Dr Andrew G Renehan PhD [a], Marcel Zwahlen PhD [c], Prof Christoph Minder PhD [c], Sarah T O'Dwyer MD [a], Prof Stephen M Shalet MD [b], Prof Matthias Egger MD [c, d]

Lancet Oncol. 2010 Jun; 11(6): 530–542.
doi: 10.1016/S1470-2045(10)70095-4
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Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studie

The Endogenous Hormones and Breast Cancer Collaborative Group‡

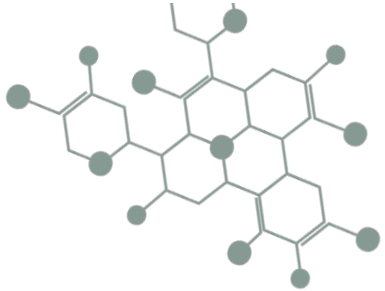
A Prospective Study of Plasma Insulin-like Growth Factor-1 and Binding Protein-3 and Risk of Colorectal Neoplasia in Women

Edward Giovannucci, Michael N. Pollak, Elizabeth A. Platz, Walter C. Willett, Meir J. Stampfer, Noreen Majeed, Graham A. Colditz, Frank E. Speizer, and Susan E. Hankinson

DOI: Published April 2000

Insulin-Like Growth Factor 1 and Prostate Cancer Risk: A Population-Based, Case-Control Study FREE

Alicja Wolk ✉, Christos S. Mantzoros, Swen-Olof Andersson, Reinhold Bergström, Lisa B. Signorello, Pagona Lagiou, Hams-Olov Adami, Dimitrios Trichopoulos



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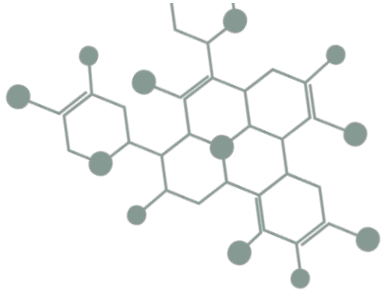
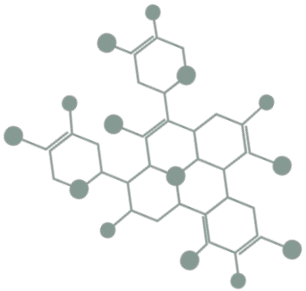
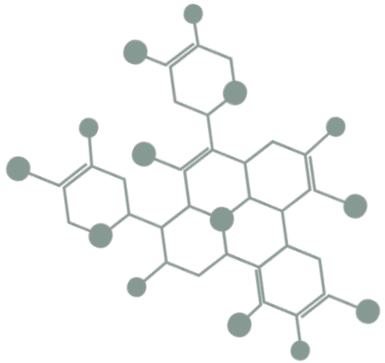


TAILOR MADE COMPOUNDING

Protection of IGF-1 BP3



Growth hormone increases production of both IGF-1 and IGFBP-3, accounting in part for the relatively high correlation between plasma IGF-1 and IGFBP-3. Because of this correlation, it is important to control for these simultaneously to observe their independent effects. Our finding that, controlling for level of IGF-1, IGFBP-3 is a strong independent protective factor may reflect binding of IGF-1, making IGF-1 not available, or direct apoptotic effects by IGFBP-3, or both **(4)** . The 3–4-fold risk differential for colorectal cancer, also observed in men in a recent analysis **(16)** , suggests a more important role for this binding protein for colorectal cancer than had been indicated for prostate **(13)** or breast cancer **(14)** .



TAILOR MADE
COMPOUNDING

Dihexa

TAILOR MADE COMPOUNDING

Dihexa

Dihexa is a peptide variant of derived from Angiotensin IV, which has been found to potently improve cognitive function in animal models. Activates C-MET.

Dihexa has been shown to enhance acquisition, consolidation, and recall of learning/memory formation.

Dihexa was found to be seven orders (10 million) of magnitude more potent than BDNF.

Most have been doing this at low doses(5-10mg). However, our Dr. Lee has talked to Dr. harding himself (who has done all of this research) and he suggested higher doses (maybe 50-75mg orally).

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Dihexa and C-Met

c-Met is a receptor tyrosine kinase belonging to the MET (MNNG HOS transforming gene) family, and is expressed on the surfaces of various cells. Hepatocyte growth factor (HGF) is the ligand for this receptor. The binding of HGF to c-Met initiates a series of intracellular signals that mediate embryogenesis and wound healing in normal cells. However, in cancer cells, aberrant HGF/c-Met axis activation, which is closely related to c-Met gene mutations, overexpression, and amplification, promotes tumor development and progression by stimulating the PI3K/AKT, Ras/MAPK, JAK/STAT, SRC, Wnt/β-catenin, and other signaling pathways. Thus, c-Met and its associated signaling pathways are clinically important therapeutic targets.

Preclinical studies have shown that in animal models, the inhibition of c-MET or neutralization of its ligand impairs tumorigenic and metastatic properties of cancer cells

To date, only a few c-MET inhibitors have entered clinical trials, however, all most all of them have shown improved results in cancer treatment.

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Dihexa and C-Met

To date, none of the Angiotensin IV variants have shown any increased cancer risk in human models or in animal studies. This includes Dihexa.

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Dihexa