Peptides to increase Growth Hormone

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Disclosure

The following potential conflict of interest relationships are germane to my presentation.

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Growth Hormone

- Growth Hormone is a hormone that stimulates growth and cell reproduction. It is a 191-amino acid, single chain protein hormone
  - Somatotropin = Growth Hormone
  - GH = Growth Hormone
  - Discovered by Dr. Li (Endocrinologist) in 1955
  - 1971 Dr. Li determined the structure of human growth hormone
My uncle- Bruce Lee
Growth Hormone Axis

Hypothalamus

GRF/SS

Pituitary

GH

Liver

IGF-1
## Stimulators and Inhibitors of GH

<table>
<thead>
<tr>
<th>Stimulatory</th>
<th>Inhibitory</th>
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</thead>
<tbody>
<tr>
<td>GHRH</td>
<td>Somatostatin “off switch”</td>
</tr>
<tr>
<td>Exercise</td>
<td>Lethargy</td>
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<tr>
<td>↑ Ghrelin</td>
<td>↓ Gherlin</td>
</tr>
<tr>
<td>↑ Amino Acids</td>
<td>↓ Amino Acids</td>
</tr>
<tr>
<td>↓ Blood glucose</td>
<td>↑ Blood glucose</td>
</tr>
<tr>
<td>↓ Fatty acids</td>
<td>↑ Fatty acids</td>
</tr>
</tbody>
</table>

Dr. Edwin Lee
Receptors - GHRH and GHS-R (Ghrelin)
Diagnosis for adult onset GH deficiency

- Screening test with IGF-1 and IGF BP3
- Insulin Tolerance Test
  - Gold Tolerance Test
  - Considered to be “dangerous”
- Glucagon Stimulation Test
- MRI to rule out a pituitary tumor

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New test for dx GH deficiency

• Dec 2017 FDA approved an orally available ghrelin agonist (GHRP)

• Macimorelin (Macrilen) is a peptide

• Macimorelin stimulates the secretion of growth hormone via the Ghrelin receptor

• 4 blood samples after the oral administration of Macimorelin


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Macimorelin (GHRP not GHRH)

- 0.5 mg/kg PO as a single dose after fasting for at least 8 hours
- Blood samples at 30, 45, 60, and 90 minutes after taking Macimorelin
- Test results are considered if the maximum serum GH level observed after stimulation is less than 2.8 ng/mL for the 4 blood draws.
Peptides
GHRH discovery from a tumor causing acromegaly

- Growth Hormone Releasing Hormone (GHRH) is a 44 amino acid peptide hormone produced in the arcuate nucleus of the hypothalamus.
- Discovery was in 1982.

Thorner M, JCEM Volume 84, Issue 12, 1 December 1999, Pages 4671-4676
Time Line


Dr. Edwin Lee
Use of rHGH vs GHRH

- rHGH is only one form of Growth Hormone, the 22 Kdalton.
- rHGH does not reproduce the normal pulsatile pattern of GH release.
- Growth hormone releasing hormone will release of 5 isoforms of Growth Hormone.
- GHRH helps reproduce the normal pulsatile pattern of GH release.
rHGH vs GHRH

- GHRH/ GHRP is more physiologic compared to rHGH
- One needs a working pituitary gland for GHRH/ GHRP to work

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Growth Hormone Releasing Hormone

- GHRH is a 44 amino acid peptide hormone
- The first part 1-29 is the active part of the hormone to stimulate Growth Hormone
- Degraded by DPP4 enzyme

Dr. Edwin Lee
GHRH receptor agonist

- CJC -1295*
- GHRH
- Modified GRF (1-29)
- Sermorelin*
- Tesamorelin*

*Dr. Edwin Lee
Sermorelin (Modified GHRH)

- Sermorelin is a synthetic version of the 1-29 amino acid of GHRH
- In 1991 Sermorelin was FDA approved for injection use to diagnosis and treatment of GH deficiency in children
- 16 children with short stature were treated with GHRH 1-29 for 9 months
- A significant improvement in height velocity was observed in the children
- SubQ 30 μg/kg per day


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Sermorelin (Modified GHRH)

- Is no longer commercially available
- Available through a compound pharmacy
- A dosage of 0.2 - 0.3 mcg of sermorelin once daily at bedtime by subQ injection

- Side effects of less than 1% include:
  - Injection site reaction, headache, flushing, dysphagia, dizziness, somnolence and urticaria

Dr. Edwin Lee
### Modified GHRH

- In the USA, the GHRH of choice has been Sermorelin.
- In Australia the GHRH of choice is CJC 1295.
- Another name for CJC 1295 is ModGRF129.
CJC- 1295 (modified GHRH)

- Is a modified GHRH 1-29
- CJC 1295 has four amino acid substitutions in GHRH(1-29) to enhance activity and render it resistant to degradation by proteolytic enzymes


- CJC 1295 has a half life of 30 minutes
- CJC 1295 with DAC (Drug affinity complex) half life is 6 days
- Sermorelin has a half life of 10-minutes


Dr. Edwin Lee
CJC- 1295 (modified GHRH)

- CJC 1295 can be compounded in two forms (DAC and non-DAC).
- Drug affinity complex (DAC) prevents enzymatic degradation thus increasing the half-life.
- Using CJC 1295-NON-DAC daily (between 6-8pm) provides a more effective GH spike at 1:00am.

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CJC-1295 (modified GHRH)
Daily Subcutaneous injection

- Study looking at doses from 30 to 250 mcg/kg
- 24 healthy adults
- IGF-I levels increased with higher dosing
- Half life about 7 days
- No serious adverse reactions were reported


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CJC 1295 DAC - 1 possible death

- CJC-1295 DAC -phase II trial for lipodystrophy in HIV patients
- July 2006 study was discontinued upon the death of one subject from a heart attack.
- 12 week study done in Argentina
- The deceased patient received the 11th weekly dose and approximately two hours later, the patient complained of chest discomfort and an ECG confirmed an acute myocardial infarction; death occurred approx 1 hour later

Dr. Edwin Lee
CJC 1295 DAC- 1 possible death

- There is no evidence of any cardiotoxic effects of CJC 1295 DAC in previous preclinical or clinical studies

- The attending physician stated that his most likely explanation for the event was the patient had asymptomatic coronary artery disease with plaque rupture and occlusion

Dr. Edwin Lee
CJC- 1295 (modified GHRH)

- Another benefit of CJC 1295 is its ability to promote slow wave sleep. Slow wave sleep is responsible for the highest level of muscle growth and memory retention.

Growth Hormone Releasing Peptides- since 1984 (not GHRH)

- Growth Hormone Releasing Peptides (GHRP) are a chemical class of Growth Hormone (GH) secretagogues that act on the hypothalamus and the pituitary to release GH.

- Growth hormone releasing peptide-6 (GHRP 6) - hexapeptide (6 amino acids) was discovered in 1984.

- GHRP 6 was the first GHRP discovered.


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Growth Hormone Releasing Peptide - GHRP not GHRH

- GH-releasing peptides (GHRP), can induce GH release from the pituitary.
- GHRP acts on Ghrelin receptor
- (originally known as GH secretagogue receptor (GHSR))

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Different GHRP - Guess which one was developed first

- GHRP-1
- GHRP-2*
- GHRP-4
- GHRP-5
- GHRP-6*
- Alexamorelin
- Ipamorelin*
- Hexarelin*
- Macimorelin*
- Ghrelin


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Another type of GHRP- Ipamorelin

- Ipamorelin is a third generation of GHRP with 5 Amino acids
- Ipamorelin increases Growth Hormone via Ghrelin receptor
- Ipamorelin lowers somatostatin levels which Increases GH

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Another type of GHRP - Ipamorelin

- Ipamorelin was originally developed by Novo Nordisk
- Ipramorelin does not raise cortisol, prolactin or aldosterone

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Peptides on the Pituitary

CJC-1295  
TESOMORELIN  
SERMORELIN  
GRF-18

IPAMORELIN  
HEXARELIN  
GHRP6  
GHRP2

Dr. Edwin Lee
CJC 1295 with Ipamorelin

- The action of CJC 1295 (modified GHRH) is potentiated by adding GHRP
- One of the most effective is Ipamorelin
CJC 1295 with Ipamorelin

- CJC 1295 non DAC with Ipamorelin
- Both are formulated at 2000 mcg/ml
- Start at 100 mcg or 0.05 ml or 5 units with an insulin syringe SQ at bedtime from Monday to Friday
- Side effect flushing for 5-10 minutes
- Can titrate to 200 mcg or 0.1 ml or 10 units SQ at bedtime Monday to Friday
- Take 2 days off per week to prevent “burn out”

Dr. Edwin Lee
Peptides on the Pituitary

CJC-1295
TESOMORELIN
SERMORELIN
GRF-18

IPAMORELIN
HEXARELIN
GHRP6
GHRP2

Dr. Edwin Lee
Other GHRP to be discussed

- GHRP-6
- GHRP-2
- Hexarelin
- All of them are cardioprotective
All of the GHRP

- All of the GHRP increase GH
- Dose-related effect with IV, intranasal, SQ and oral administration.
- The GH-releasing activity of GHRPs is synergistic with that of GHRH
- Intravenous bolus GHRP releases more GH than GHRH in humans
- GHRPs are pleiotropic peptides with major effects on GH, nutrition, cardiovascular and metabolism


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All of the GHRP

• High dose of GHRP down regulates responsiveness of the GH axis

• Low dose of GHRP can maintain elevated GH secretion and IGF-I

All of the GHRP

- In the cardiovascular system the highest GHRP binding capacity was found in ventricular myocardium

GHRP-6 (studies from 1984)

- Peptide of 6 Amino acids (His-DTrp-Ala-Trp-DPhe-Lys-NH2)
- Can be delivered IV intranasal/ SQ/ Oral
- Since it activates the Ghrelin receptor it increases hunger
GHRP-6 - half life

- Half life of GHRP-6 is 2.5 hours
- GHRP-6 was mostly excreted unchanged and detected in urine 23 h after administration

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GHRP-6 testing

- GHRP-6 has been compared to the insulin tolerance test to diagnose GH deficiency
- 49 patients with hypothalamic or pituitary disease
- GHRP-6 alone as a provocative test is highly specific, but with limited sensitivity for the diagnosis of GH deficiency

**GHRP-6 on IGF-1**

- GHRP-6 has been shown to increase GH
- Dose at 1 mcg/kg (IV)
- Intranasal GHRP-6 (30 mcg/kg) increases IGF-1 from 94 to 126 mcg/L
- One study showed that GHRP-6 had no increase in IGF-1

*Dr. Edwin Lee*
GHRP-6 – Cardiac benefits

- GHRP-6 has shown to reduce myocardial necrosis and exhibit antioxidant effects in a model of acute myocardial infarction.

- Study done in pigs 400 mcg /kg

- Infarct mass and thickness were reduced by 78% and 50% respectively

Dr. Edwin Lee
GHRP-6, GHRP-2, and Hexarelin 2 Cardiac receptors

- GHS-R1 : (Growth hormone Secretagogue receptor type 1 a)
- CD36
- Activation of the 2 receptors are cardiotrophic

- 21 day pre therapy with GHRP-6 prevented sudden death in dogs with dilated cardiomyopathy subjected to acute ischemia.
- 100% survival vs 50% survival with GH

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GHRP-6 Prolactin and cortisol

- IV Bolus of (1 mcg/kg) GHRP-6 increase Cortisol and Prolactin
  - Prolactin from 5.7 to 8.6 mcg/L
  - Cortisol from 12 to 18 mcg/dL
- Did not affect FSH, LH, Insulin ,TSH and glucose

- IV Bolus of (0.1 and 0.3 mcg/kg) GHRP-6 did not increase cortisol or prolactin
- Did not affect LH, FSH, TSH and ACTH


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GHRP-6 dosing

- Oral dosing

- Several studies at 300 mcg/kg
  
  
  

- Subcutaneous

- Dosing 1 mcg/kg (Saturated dose)

- 100 mcg SQ qhs 5 out 7 nights a week


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GHRP 2 - second generation

- GHRP-2 developed at Tulane University led by Dr Cyril Bowers
  - No author, Drugs R D. 2004;5(4):236-9
- More potent than GHRP-6
GHRP-2 (not GHRH)

- Peptide of 6 Amino acids- known as Pralmorelin
- Can be delivered IV, intranasal, SQ, oral
- Since it activates the Ghrelin receptor it increases hunger


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GHRP-2 on IGF-1

- GHRP-2 can be detected in urine up to 47 h after administration

- Few studies show that GHRP-2 increases IGF-1

- 17 patients received 30 days of subcutaneous infusion of GHRP-2 via pump (1 mcg/kg/h) increased IGF-1 and IGF-BP3

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Combo of GHRH with GHRP-2


Young Women (N = 7)

Mean GH Conc.

IV GHRP-2 (0.1 μg/kg) + GHRH (1.0 μg/kg)

[499]

IV GHRH (1.0 μg/kg)

[146]

IV GHRP-2 (0.1 μg/kg)

[97]
GHRP-2 stimulates Growth Hormone in mutated GHRH receptor

- Growth hormone-releasing peptide-2 stimulates GH secretion in *GH-deficient patients with mutated GH-releasing hormone receptor*

- 11 individuals with isolated GH deficiency (GHD) due to a homozygous mutation of the GHRH receptor (GHRH-R) gene

- No change in cortisol, ACTH or prolactin

Dr. Edwin Lee
Peptides on the Pituitary

- CJC-1295
- TESOMORELIN
- SERMORELIN
- GRF-18

- IPAMORELIN
- HEXARELINV
- GHRP6
- GHRP2

Diagram showing the interaction of peptides with the pituitary gland, including GHRH, GHS (synthetic), and Ghrelin (natural). The diagram illustrates the regulation of GH (growth hormone) production through cAMP and calcium ion ([Ca^{2+}]_i) pathways.
GHRP-2 study (SQ) in GH deficient children
Mericq V et al. J Clin Endocrinol Metab. 1998 Jul;83(7):2355-60

- 6 children w/ growth failure
- GHRP-2 stepwise dosing of SC doses 0.3 to 3 mcg/kg/d
- Stimulated GH but IGF-1 and IGFBP-3 did not change
- Growth velocity was higher with GHRP-2
- No side effects
GHRP-2 study (Intranasal) in GH deficient children

- 15 children with short stature
- Intranasal GHRP-2, 5-15 micrograms/kg, twice a day for 3 months then TID
  - (dose of 10 mcg/kg - 50 kg = 500 mcg TID= total dose of 1500 mcg/day)
- Height velocity increased from 3.7 cm/year to 6.1 cm/year at 6 months
- No significant changes in IGF-1

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GHRP-2 Anorexia

- In Japan GHRP-2 used as a diagnostic agent
- Case study of using GHRP-2 in a 38 year old woman with 20 year history of anorexia nervosa
- Intranasal Rx for 1 yr

- Dose of 1 nasal spray before meals and at bedtime
- 1 spray = 100 ug
- Later increased to 2 nasal sprays before meals and 1 spray at bedtime for 10 months (700 mcg a day)


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GHRP-2 Anorexia


- Increased by 6.7 kg (from 21.1 kg to 27.8 kg) in 14 months after starting GHRP-2 administration
- The fatigability and muscle strength, physical and mental activities all increased
- Increase in IGF-1
- No side effects seen

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GHRP-2-healthy men

- GHRP-2 increases food intake in healthy men
- infused 7 lean, healthy males with GHRP-2 (1 microg/kg/h) for 270 minutes
- Increased appetite by 36%

GHRP-2 – Cancer anorexia cachexia

- GHRP-2 (Sq 10 mcg/kg) reverses anorexia with chemotherapy in mice
- Increase survival
- GHRP-2 may improve the quality of life of cancer patients

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GHRP-2 - Cardioprotective

- Pretreatment GHRP-2 directly protects against the diastolic dysfunction of myocardial stunning in rabbit heart model

- GHRP-2 reduced the progression of left ventricular dysfunction in dilated cardiomyopathic hamsters.

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GHRP-2 on Cortisol and Prolactin

• GHRP-2 in 30 day Subcutaneous infusion did not increase cortisol but increased prolactin*.

• *Increase of Prolactin from 12 to 16 (mcg grams/l all within normal range)

• Bowers CY, et al. JCEM 2004 89(5):2290-2300
GHRP-2 - dosing

- Suggested dosing
- 200 mcg SQ qhs 5 out 7 nights a week
- Transdermal 200 mcg/ml apply 1 ml or 200 mcg 5 out 7 nights a week

- Anorexia case study
- Dose of 1-2 nasal spray before meals and at bedtime
- 1 spray = 100 ug
- (700 mcg a day)

Hexarelin (GHRP not GHRH)

- Peptide of 6 Amino acids
- Can be delivered IV, oral intranasal/ SubQ
- Although it activates the Ghrelin receptor it does not increase hunger

Hexarelin - second generation

- Hexarelin via IV, intranasal, oral and subcutaneous increases GH
  - Similar potency of GHRP-2

- Half-life of 55 min
- Mild elevation of IGF-1
# Hexarelin: Improving Growth Hormone

Imazio, M et al. Eur. J. Heart Fail. 4:185-191

## Table 1
Basal and peak GH levels after hexarelin administration

<table>
<thead>
<tr>
<th>Group</th>
<th>Basal GH (µg/l)</th>
<th>Peak GH (µg/l)</th>
</tr>
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<tbody>
<tr>
<td>Dilated CMP</td>
<td>0.2 ± 0.1</td>
<td>37.1 ± 12.7</td>
</tr>
<tr>
<td>Ischemic CMP</td>
<td>0.2 ± 0.1</td>
<td>31.5 ± 14.8</td>
</tr>
<tr>
<td>Normal subjects [41]</td>
<td>0.2 ± 0.1</td>
<td>56.0 ± 14.4</td>
</tr>
<tr>
<td>GHD patients [41]</td>
<td>0.0 ± 0.0</td>
<td>1.9 ± 0.9</td>
</tr>
</tbody>
</table>

*Abbreviations: GHD, GH-deficiency; CMP, cardiomyopathy.*
Hexarelin - Bone loss

- Hexarelin improves bone density in gonadectomized male and in ovariectomized female rats


Dr. Edwin Lee
Hexarelin - Improves Insulin Resistance 2017

• Significantly improved glucose and insulin intolerance and decreased plasma and liver triglycerides

• Increase in lean mass

• Study done in Insulin resistant MKR mice

Hexarelin – Cardiovascular benefit
Mouse model of acute myocardial infarction

- Hexarelin treatment (pre and post 0.3 mg/kg/day) preserves myocardial function
  - significant improvement in LV function after 14 days treatment.

- Hexarelin treatment (pre and post 0.3 mg/kg/day) reduces cardiac fibrosis

- Reduces TGF-1 expression

- Reduces troponin-I, IL-1b and TNF-a level

Dr. Edwin Lee
Hexarelin - Cardiovascular benefit

Imazio, M et al. Eur. J. Heart Fail. 4:185-191

- Study of 8 subjects with dilated cardiomyopathy and 5 with ischemic cardiomyopathy
- IV bolus of 2 mcg/kg

- Left ventricular function improved in ischemic cardiomyopathy but not in dilated cardiomyopathy subjects

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**Hexarelin** Cardiovascular benefit in 30 min

Imazio, M et al. Eur. J. Heart Fail. 4:185-191

<table>
<thead>
<tr>
<th>Group</th>
<th>LVEF (%)</th>
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<tbody>
<tr>
<td></td>
<td>Basal</td>
</tr>
<tr>
<td>Dilated CMP</td>
<td>16.7 ± 2.1</td>
</tr>
<tr>
<td>Ischemic CMP</td>
<td>22.6 ± 2.1</td>
</tr>
<tr>
<td>Normal subjects [41]</td>
<td>64.0 ± 1.5</td>
</tr>
<tr>
<td>GHD patients [41]</td>
<td>50.0 ± 1.9</td>
</tr>
</tbody>
</table>

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Hexarelin - on Cortisol and Prolactin

- IV use Hexarelin increases ACTH, Cortisol and Prolactin

- Intranasal and oral Hexarelin does not increase cortisol and prolactin

- For SQ use of Hexarelin (1.5 micrograms/kg) twice a day for 16 weeks does not increase ACTH, cortisol and prolactin

- Oral, Intranasal and SQ does not increase ACTH, cortisol and prolactin

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Hexarelin - Dosing

- Suggested Dosing
- 100 to 200 mcg SQ qhs 5 out 7 nights a week
- 100-200 mcg SQ daily at bedtime and consider taking 1 month off after 3 months of Hexarelin
HOT STUFF
Tesamorelin - GHRH

- Tesamorelin, developed by the Canadian pharmaceutical company Theratechnologies
- Tesamorelin (brand name Egrifta)
- Stabilized against dipeptidyl peptidase IV (DPP4) degradation
  - Half life of 30 minutes
  - GHRH half life of 7 min

Dr. Edwin Lee
Tesamorelin- GHRH

• 44 amino acids of human GHRH with the addition of a trans-3-hexenoic acid group

• formerly known as TH9507

• Tesamorelin (brand name Egrifta)
Tesamorelin- GHRH

- 2010 FDA approves Tesamorelin for HIV lipodystrophy
Tesamorelin- GHRH

• Harvard Study- in Healthy Men

• Tesamorelin 2 mg sc once daily for 2 wk

• Raises IGF-1 level by 182


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<tr>
<th></th>
<th>Baseline</th>
<th>2 week</th>
<th>4 week</th>
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<tbody>
<tr>
<td>IGF-1</td>
<td>148</td>
<td>329</td>
<td>161</td>
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</table>
Tesamorelin - GHRH

- Reduces Triglycerides
- Reduces Visceral Adipose Tissue
- Reduces Carotid Intima Media Size
- Improves Cognition in people over 60 years

Tesamorelin - Dosing Protocol

- 1 mg injected at bedtime subcutaneously 5-6/7 days a week

- Compounded with Trehalose instead of Manitol

Dr. Edwin Lee
Conclusion

- The GH-releasing activity of GHRPs is synergistic with that of GHRH
- GHRPs are pleiotropic peptides with major effects on GH, nutrition, cardiovascular and metabolism
- Generally very well tolerated
- Use the Peptides at bedtime
- Recommend to take it 5 nights a week
Thank You