

aegis

16870 W. Bernardo Drive,
Suite 390
San Diego, CA 92127
Phone: 858-618-1400
Facsimile: 858-618-1441
www.aegisthera.com

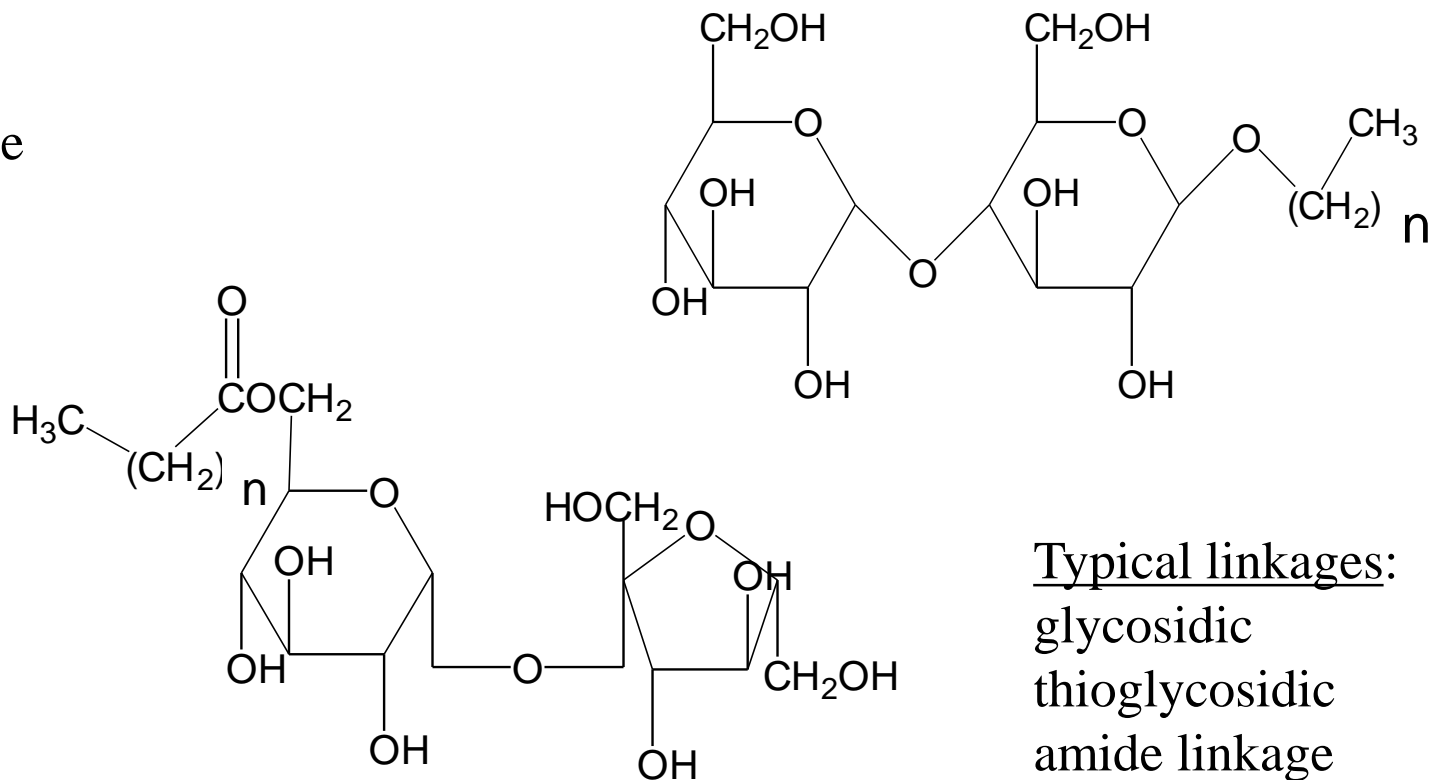
Therapeutics

**“Novel Formulations for
Non-Invasive Delivery of Peptides
and Small molecule Drugs”**

Intravail®/ProTek® Technologies - Based on Alkylsaccharides (sugar + alkyl chain - various linkages)

Typical oligosaccharides:

maltose
maltotriose
maltotetraose
sucrose
trehalose
sucrose
trehalulose
turanose
maltulose
leucrose
palatinose
isomaltose
maltitol



Typical linkages:

glycosidic
thioglycosidic
amide linkage
ureide
ester

Typical alkyl chain lengths:

10-18 carbons

General Intravail® /ProTek® Characteristics

- Safe, odorless, tasteless, non-toxic, non-mutagenic, and non-irritating
- Synthetic pure chemical entities prepared under GMP
- Provides unmatched bioavailability - comparable to subcutaneous injection, via the intranasal and other mucosal membrane administration routes (up to ~30KDa MW)
- Allows controlled transient mucosal permeation by both paracellular (tight-junction) and transcellular routes
- Soluble in water or oils - compatible with routine liquid formulation and dispensing processes for ease of scale-up and production
- Shown to be highly effective (orally) for BCS Class III/IV small peptides and small molecules
- Shown to greatly increase oral bioavailability in tablets, oils (i.e., soft-gel compatible), and flash-dissolve oral (Zydis®-like) formats

Multiple Modes of Transmucosal Delivery for Macromolecular Drugs



Metered spray pumps

➤ Nasal



Gelcaps

Tablets

➤ Oral (gastrointestinal)



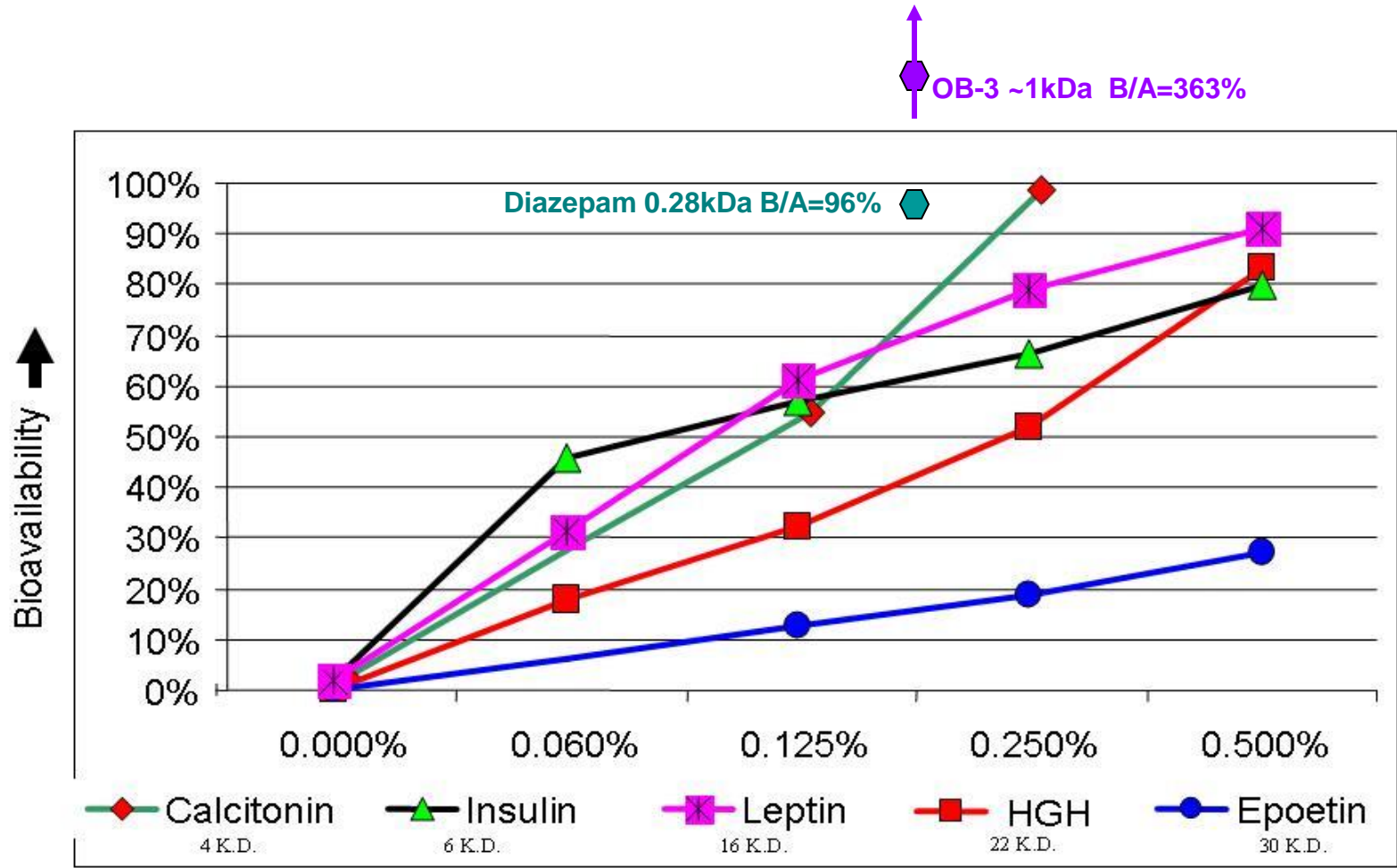
Flash dissolve



Edible films

➤ Oral cavity (buccal, sublingual)

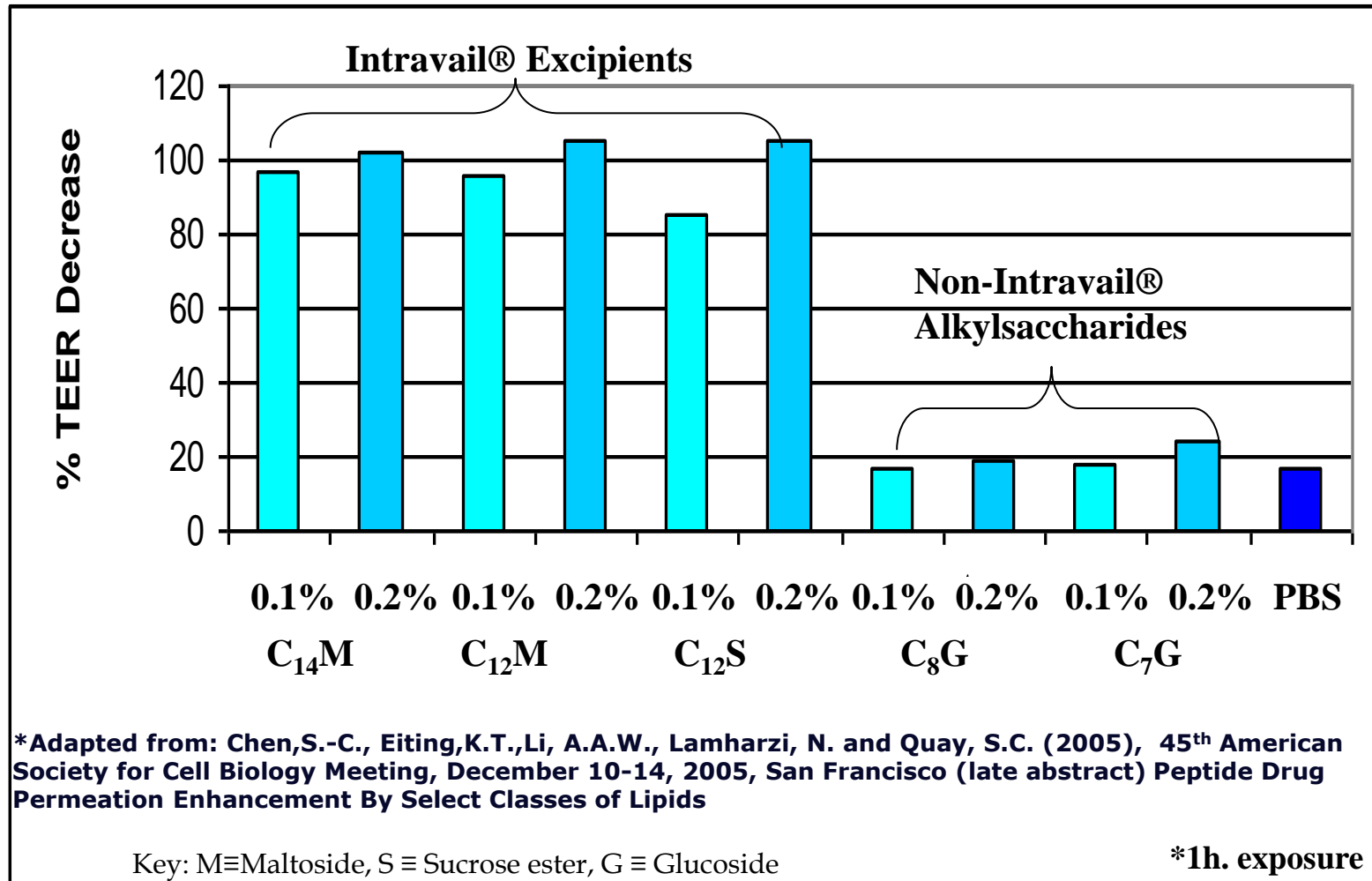
Intravail® Provides Intranasal Bioavailability Comparable to Injection



Intravail® Concentration
Sprague Dawley® rats; calcitonin i.v., all others sub-Q

Paracellular Absorption: Reduction in TEER*

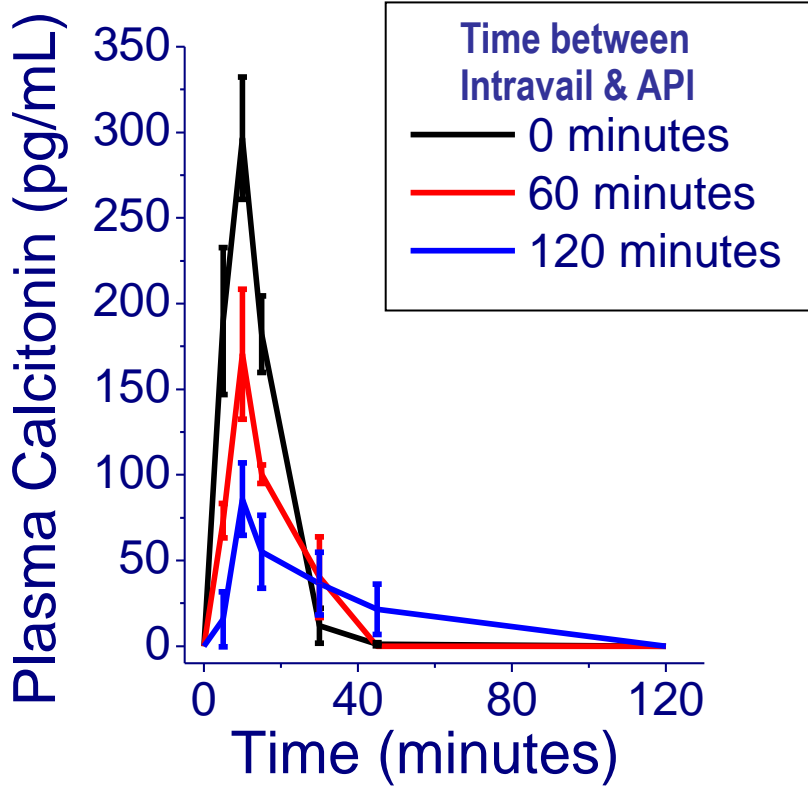
(Normal Human Tracheal/Bronchial Epithelial Cell Derived Mucociliary Tissue)



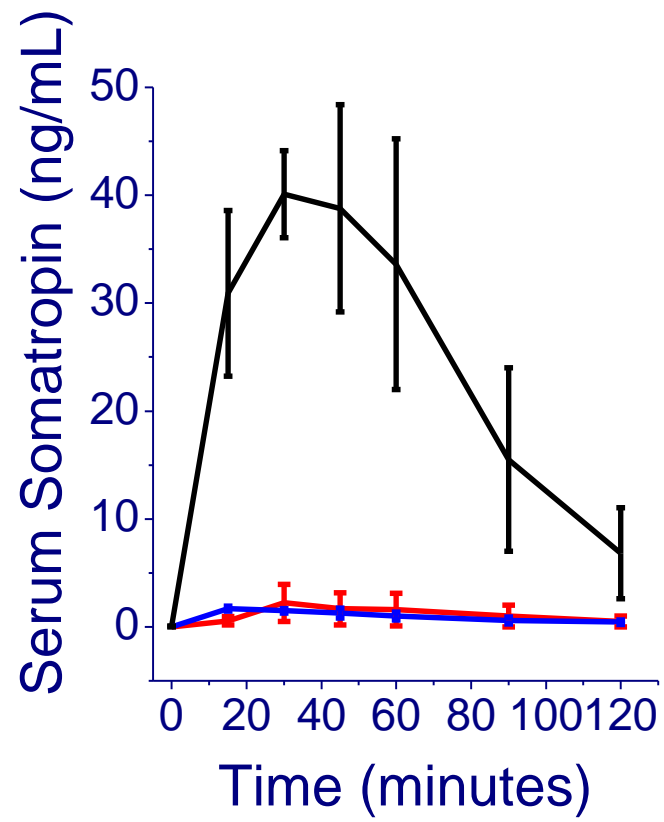
Intravail® Interacts With Nasal Mucosa – Not Drug

Rat Model Data

Calcitonin



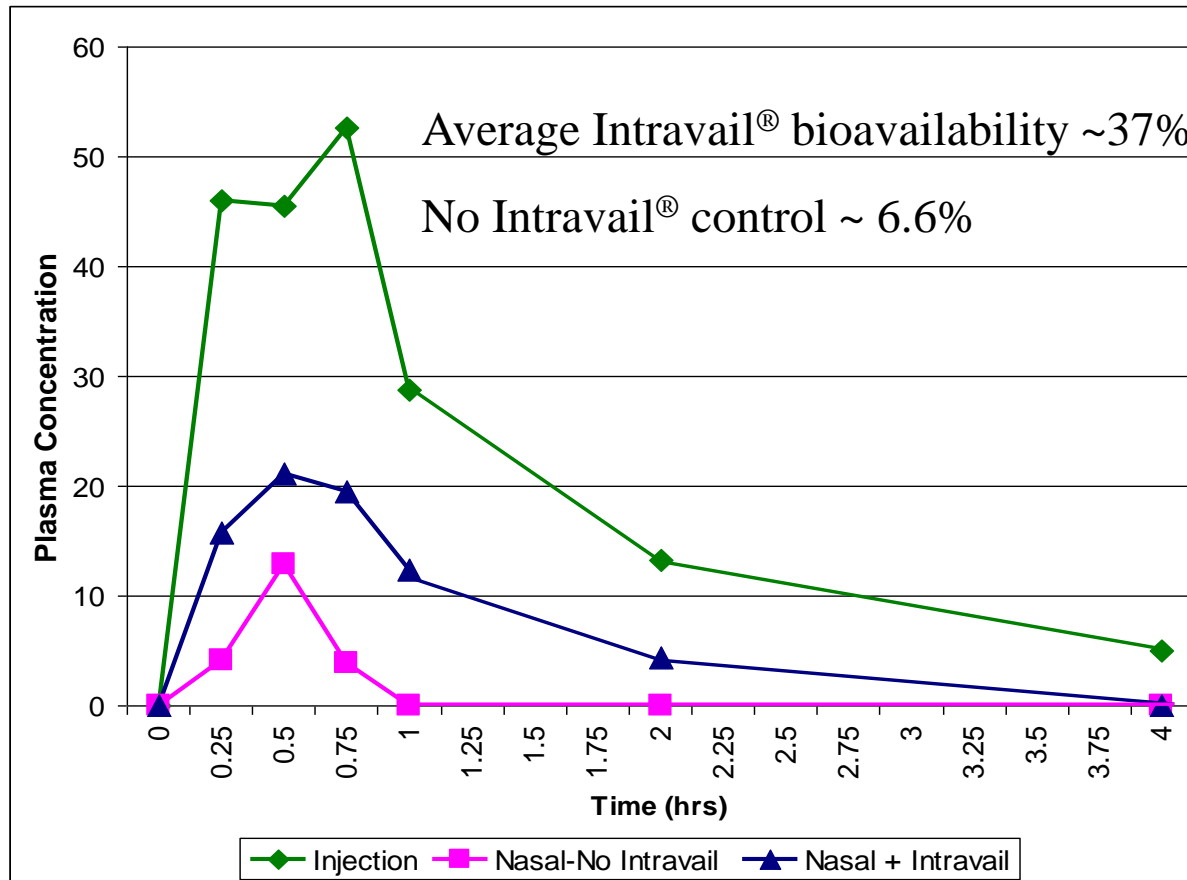
Somatotropin



Arnold, Fyrberg, Meezan, Pillion (2010) J Pharm Sci. 99(4):1912-20.

3-Way Human Crossover Study — Intravail® Increases Calcitonin Bioavailability >5-fold

Mean Plasma Drug Concentration vs. S.C. Injection in 10 Healthy Females



Maggio, Meezan, Ghambeer, and Pillion (2010) Drug Del Tech. 2010;10:58–63.

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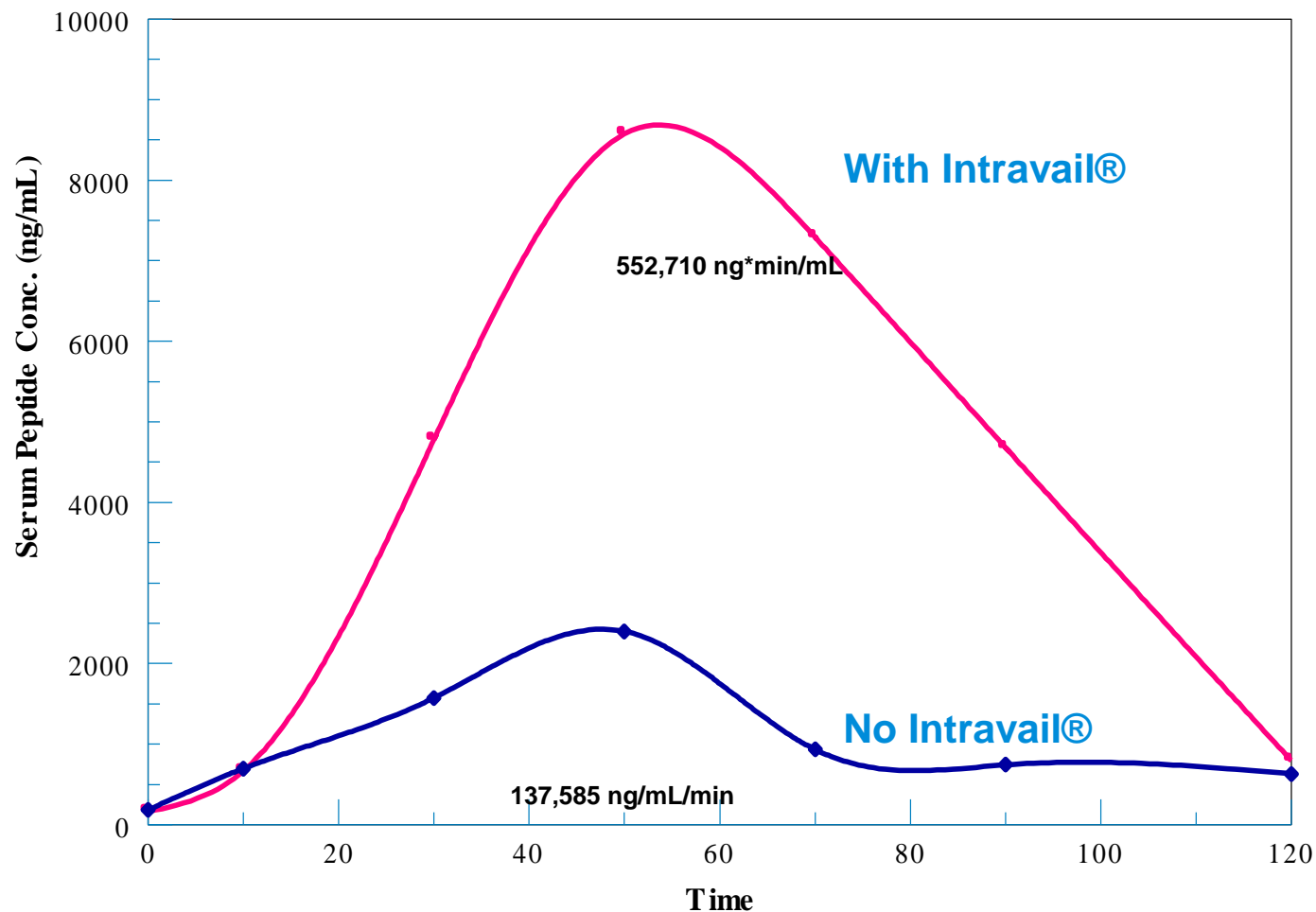
[D-Leu-4]OB3 – First Orally Active Weight Loss & Anti-Diabetic Peptide

10

- Patented (7-mer peptide) leptin derived fragment
- Reduces weight gain & food intake in mouse obesity models
- Normalizes blood glucose in mouse diabetes/obesity models
- Increases osteocalcin – may prevent/reverse bone loss associated with weight loss & osteoporosis
- High oral bioavailability (56% w. Intravail[®])
- High nasal bioavailability ($\geq 100\%$ w. Intravail[®]) – for rapid onset
- Multiple issued patents*

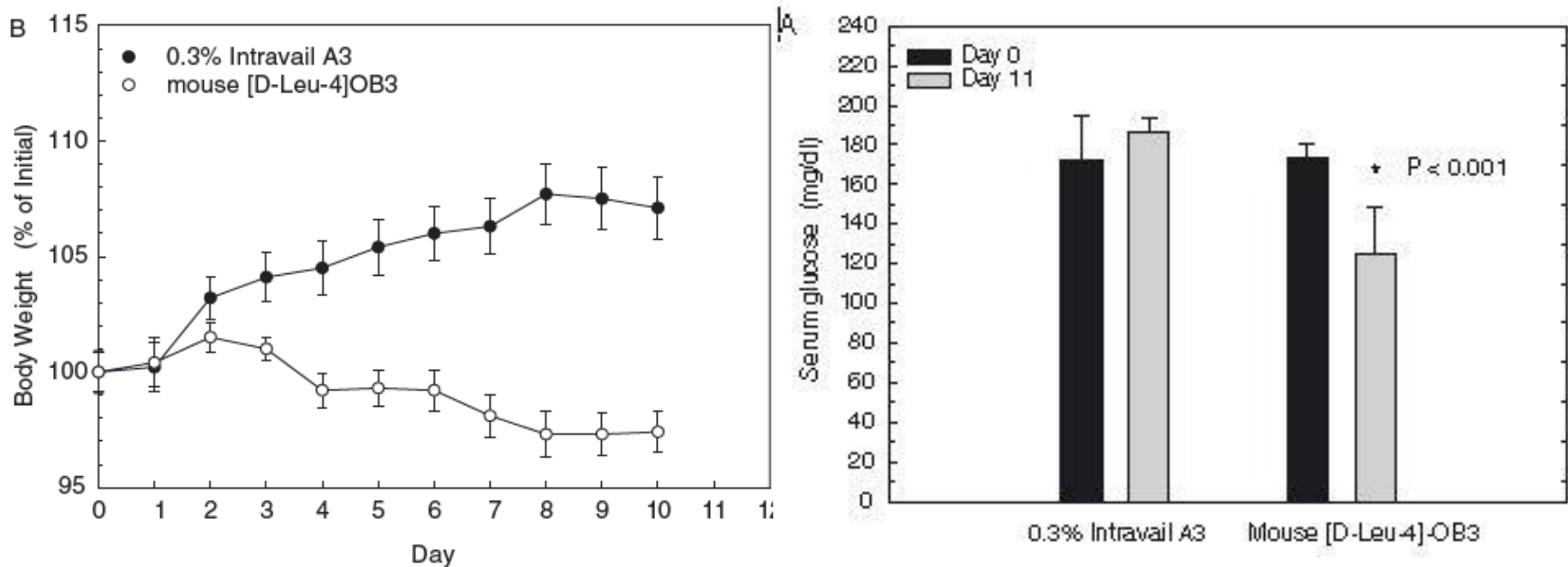
* Dr. Patricia Grasso et al., Albany Medical College

Oral Delivery of [D-leu-4]OB3 Anti-Obesity Peptide in Rodents (~1kD MW)



Lee et al. Regulatory Peptides 160 (2010) 129–132

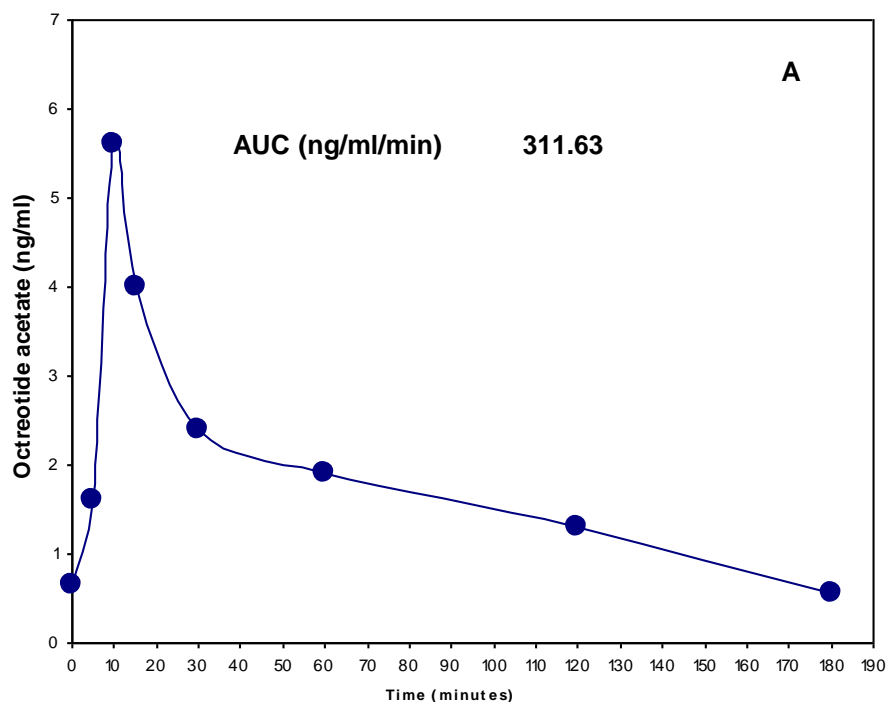
Oral OB-3 Administration - Body Weight Gain and Serum Glucose in ob/ob Mice



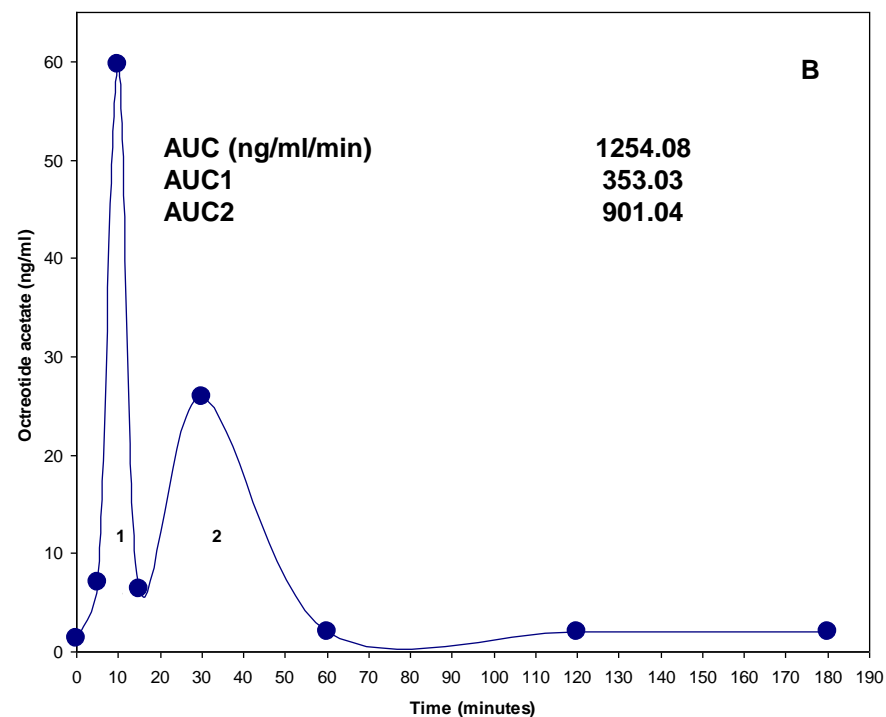
Novakovic, Grasso, et al. Diabetes Obes Metab. (2010) 12(6):532-9.

Oral Bioavailability with Intravail[®] Exceeds That of S.C. Injected Octreotide

Uptake of 30ug Octreotide in PBS s.c.



Oral Uptake of 30ug Octreotide in Intravail[®]



Maggio & Grasso Regulatory Peptides 167 (2011) 233–238

Human Clinical Data

- Nasal sumatriptan
 - Six human trials to date
 - T_{max} reduced to 8 min. from 60-120 min. for Imitrex
 - Therapeutic drug levels equivalent to Imitrex achieved in 2-3 min.. (i.e., 20X – 30X faster)
 - Licensee – a Top-10 multinational generics company
- Nasal diazepam
 - Nasal spray designed as an alternative to the Diastat rectal gel
 - Bioequivalent to Diastat
 - 96% absolute bioavailability
 - Licensee – Neurelis Inc. (San Diego)
- Nasal PTH 1-34 (~4000 Da)
 - Nasal spray
 - Three phase 1 trials completed: single dose/7 day b.i.d, and 6 weeks b.i.d.
 - Approximately 30% nasal bioavailability compared to Forteo injection
- Oral endocrine peptide (~1000 Da)
 - Formatted as a 3 sec. flash dissolve (Zydis) wafer
 - 14 patient feasibility study completed

Intravail® Summary

- Unmatched intranasal bioavailability (up to ~30kD)
- Unmatched oral bioavailability for certain peptides
- Rapid onset of action
- Greater patient convenience and compliance
- Elimination of needle stick injuries/infections
- Avoidance of gastric hydrolysis & “first pass effect”
- Compatible with “off-the-shelf” metered nasal spray devices & oral tablet/capsule/flash-dissolve formats

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Contact Information:

Edward T. Maggio, Ph.D., Chief Executive Officer
emaggio@aegisthera.com

Ralph R. Barry, Chief Business Officer & CFO
rbarry@aegisthera.com