Emerging Opportunities

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Disclosures

- Medical Advisory Board Medifast
- Medical Advisory Board Tanita Corp.
\[ \%\text{Fat} \propto \text{BMI} \]

\[ = \text{Genes} + \text{Epigenes} + \text{Environment} + G \times \text{Epig} + G \times \text{Environ} + \text{Epig} \times \text{Environ} \]
Leptin Mutations: Targeted Pharmacotherapy
MC4R Mutations: 2 - 5% of Severe Obesity

Peptide Therapeutics

Semaglutide (Novo Nordisk): Long acting GLP-1 agonist for 1X/Week injection

GLP-1: Glucagon-Like Peptide 1
Challenges of Oral Peptide Delivery

Oral version of semaglutide co-formulated with absorption enhancer SNAC which causes localized pH increase leading to higher solubility and protection from enzymatic degradation.
Oral Peptides: Semaglutide

Baseline 92 kg

Weight loss (kg)

Time (weeks)

Placebo

SC

Oral

52 weeks
Combination Peptides

GLP-1 agonist

GLP-1R/GcgR co-agonist

GLP-1R/GIP/GcgR triple agonist

Glucagon-like peptide 1

Pocai, Diabetes 58, 2009
Peptides in Development

- 23+ GLP-1 peptides in development:
  - Oxyntomodulin (GLP-1/glucagon co-agonist peptide)
  - GLP-1-Fc-FGF21; also FGF21 alone
  - GLP-1-GIP
  - With glucagon analog
  - Long-acting preparations

Peptide YY and NPY analogs
New Oral Medication Combinations

- 4 in development
- Dual SGLT1 and SGLT2 inhibitor
- Combination treatments
  - Dapagliflozin + Exenatide
  - Canagliflozin + Phentermine

*Phase II Weight Loss Efficacy
Canagliflozin/Phentermine Combination*

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Placebo</th>
<th>Canagliflozin 300mg</th>
<th>Phentermine 15mg</th>
<th>Canagliflozin 300mg + Phentermine 15mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>-1%</td>
<td>-1%</td>
<td>-1%</td>
<td>-1%</td>
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<tr>
<td>12</td>
<td>-2%</td>
<td>-2%</td>
<td>-2%</td>
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<tr>
<td>18</td>
<td>-3%</td>
<td>-3%</td>
<td>-3%</td>
<td>-3%</td>
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<tr>
<td>26</td>
<td>-5%</td>
<td>-5%</td>
<td>-5%</td>
<td>-5%</td>
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</table>

Hollander et al, 2016.06.12, ADA 76th Scientific Sessions, abstract 319-LB
Targeting Hedonic Mechanisms

μ-opioid receptor inverse agonist

Combine with bupropion

Mol Psychiatry. 2014;19:1341
Advances in Target Discovery

- Modular “omic” components
  Patient and Normal Data

- Molecular networks & pathways

- Compound Knowledge Base

- Candidate compounds assigned based on network analysis

- Network biomarkers & disease drivers

- Predicting compound synergies/combinations

- Candidate compound combinations

- Chemical Biology and Validation

- Clinical Validation
## Devices: Gastric Balloon Systems

<table>
<thead>
<tr>
<th>Study Week</th>
<th>ORBERA™ %TBWL</th>
<th>95% CI</th>
<th>Control %TBWL</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>0.9%</td>
<td>0.7–1.2</td>
<td>0%</td>
<td>-0.2–0.2</td>
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<tr>
<td>Week 1</td>
<td>3.5%</td>
<td>3.1–3.8</td>
<td>0.9%</td>
<td>0.5–1.2</td>
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<tr>
<td>Week 2</td>
<td>4.1%</td>
<td>3.8–4.5</td>
<td>1.4%</td>
<td>1.1–1.8</td>
</tr>
<tr>
<td>Week 4</td>
<td>5.5%</td>
<td>5.1–6.0</td>
<td>2.1%</td>
<td>1.5–2.7</td>
</tr>
<tr>
<td>Week 8</td>
<td>7.0%</td>
<td>6.4–7.6</td>
<td>2.6%</td>
<td>2.1–3.2</td>
</tr>
<tr>
<td>Week 12</td>
<td>7.9%</td>
<td>7.2–8.7</td>
<td>3.1%</td>
<td>2.5–3.8</td>
</tr>
<tr>
<td>Week 16</td>
<td>8.4%</td>
<td>7.5–9.3</td>
<td>3.3%</td>
<td>2.5–4.0</td>
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<tr>
<td>Week 20</td>
<td>8.8%</td>
<td>7.8–9.8</td>
<td>3.4%</td>
<td>2.6–4.2</td>
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<tr>
<td>Week 24</td>
<td>9.1%</td>
<td>8.1–10.2</td>
<td>3.3%</td>
<td>2.5–4.2</td>
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<tr>
<td>Week 26</td>
<td>10.2%</td>
<td>9.0–11.4</td>
<td>3.3%</td>
<td>2.4–4.2</td>
</tr>
<tr>
<td>Week 39</td>
<td>9.1%</td>
<td>7.9–10.3</td>
<td>3.4%</td>
<td>2.4–4.3</td>
</tr>
<tr>
<td>Week 52</td>
<td>7.6%</td>
<td>6.2–8.9</td>
<td>3.1%</td>
<td>2.0–4.1</td>
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### Primary Effects

<table>
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<tr>
<th>Primary Endpoint #1</th>
<th>%EWL at 24 Weeks</th>
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<tbody>
<tr>
<td>Intent-to-Treat Population</td>
<td>256 (21.95, 28.21%)</td>
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Endobarrier

Weight loss and diabetic improvement

**Weight:**

- Weight: 
  - D0: 130 kg, W24: 110 kg, P < 0.001
  - Excess Weight: 
    - D0: 100%, W24: 75%, P < 0.001

**Diabetes:**

- HbA1c:
  - D0: 9%, W24: 8%, P < 0.001

Reduction of anti-diabetic medication in 16/17 patients
ABC Model of Behavioral Obesity Management

We help employers and health plans tackle chronic disease in the most engaging, effective, and scalable way possible.

Mexico sugary-drink purchases:
-5.5% year 01
-9.7% year 02
Certification and Training Programs