Novel Therapeutic for Healing Gut Tissue

DDE Presentation June 28, 2018
# Experienced Team, Focused on Executing

<table>
<thead>
<tr>
<th>Name</th>
<th>Title/Role</th>
<th>Previous Experience</th>
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<tbody>
<tr>
<td><strong>Artin Asadourian</strong></td>
<td>Co-Founder, President &amp; CEO</td>
<td>Former Amylin, Amgen, Bayer, Wyeth</td>
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<tr>
<td><strong>Soumitra S. Ghosh</strong></td>
<td>Co-founder &amp; CSO</td>
<td>Former Amylin, BMS, MitoKor, Baxter</td>
</tr>
<tr>
<td><strong>Karl Sylvester, MD</strong></td>
<td>CMO</td>
<td>Pediatric Surgeon – Stanford Children’s Hospital&lt;br&gt;Associate Dean Maternal Child Health- Research Professor of Surgery and Pediatrics&lt;br&gt;Stanford University School of Medicine</td>
</tr>
<tr>
<td><strong>David C. Litzinger</strong></td>
<td>CMC Lead &amp; Scientific Advisor</td>
<td>Former Amgen, Lilly, Ambrx, Amylin, Allergan</td>
</tr>
<tr>
<td><strong>Harry Leonhardt</strong></td>
<td>Legal &amp; IP Advisor</td>
<td>Former Amylin Sr. VP, Deputy General Counsel and Corp. Secretary</td>
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## SCIENTIFIC ADVISORS

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<tr>
<th>Name</th>
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<tr>
<td><strong>Mark Frey PhD</strong></td>
<td>Inventor</td>
<td>The Saban Research Institute&lt;br&gt;Children’s Hospital Los Angeles</td>
</tr>
<tr>
<td><strong>Tachi Yamada, MD</strong></td>
<td>Former Executive Vice-President, Chief Medical and Scientific Officer of Takeda Pharmaceuticals</td>
<td></td>
</tr>
<tr>
<td><strong>William Sandborn MD</strong></td>
<td>Chief, Division of Gastroenterology&lt;br&gt;UC San Diego, Inflammatory Bowel Disease</td>
<td></td>
</tr>
<tr>
<td><strong>Mark Underwood, MD</strong></td>
<td>Chief of Neonatology&lt;br&gt;UC Davis Neonatology</td>
<td></td>
</tr>
<tr>
<td><strong>Arthur D’Harlingue, MD</strong></td>
<td>Attending Neonotologist, Children’s Hospital Oakland</td>
<td></td>
</tr>
<tr>
<td><strong>Larry Moss, MD</strong></td>
<td>Surgeon-in-Chief, Nationwide Children’s Hospital&lt;br&gt;Pediatric Surgeon&lt;br&gt;Ohio State University</td>
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Neuregulin-4 Asset

- Naturally occurring physiological peptide
- Present in maternal breast milk and the GI tract
- Folded peptide (62 aa, 3 disulfides) with high chemical and metabolic stability
- Selective ligand for ErbB4 receptor that is expressed in the GI tract and pro-inflammatory M1 macrophages
- Exhibits novel protective and restorative effects on intestinal tissue.
- No mitogenic effects
- Oral delivery - ideally suited for targeted gut mucosal healing action.
- Targeted GI disorders include Crohn’s disease, ulcerative colitis and necrotizing enterocolitis.
- Licensed from Children’s Hospital Los Angeles
The Progression of Compromised Gut Tissue

PREEMIES
Immature Gut
Necrotizing Enterocolitis and Sepsis
30% Incidence

ADULTS
Gut Affected by Crohn’s Disease or Ulcerative Colitis

INFLAMMATION and INFECTION to INTESTINAL INJURY

IBD
1.4M Affected Adults in the U.S.
Novel Platform Biologic Applicable to Multiple Diseases

**CRITICAL NEED**

NEC / Sepsis

No available therapies for treatment or prevention, high mortality and life long complications

**Driven by Common Disease Biology**

Pass Through Common Pathways of Inflammation and Cellular Injury

No Available Products That Promote Clinically Desired Mucosal Healing

**NRG-4**

Direct HEALING of Injured Gut Mucosa

Preparing for IND Enabling and Clinical POC Studies

**UNMET NEED**

IBD

Frontline drugs do not target mucosal healing, have high non-response rates, and become refractory over time
## A Novel Therapeutic for Unmet Needs in IBD

### Frontline Therapeutics

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<th>Enable <strong>INDIRECT</strong> Healing by Dampening Inflammation</th>
<th>NRG-4</th>
<th>Enable <strong>DIRECT</strong> Healing via protection of Enterocyte and Paneth Cells</th>
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**NRG-4**

Frontline Therapeutics

- **Enable INDIRECT Healing**
  - Dampening Inflammation
  - Limited to anti-inflammatory
  - No direct mucosal integrity nor regenerative effects
  - Significant co-morbidities, including increased risk of infections
  - Significant rate of non-responders and progression of disease
  - Biologics are infusions or injectables

- **Enable DIRECT Healing**
  - Via protection of Enterocyte and Paneth Cells
  - Specific M1 macrophage innate immunity target
  - Direct mucosal integrity effects
  - Naturally occurring peptide with single receptor and no mitotic effects
  - 1st in class, novel biologic with multi-faceted MOA
  - Potential for oral therapy
IBD: A Prevalent Disease with Unmet Needs

IBD Patient Population

1.4M AMERICANS

2.2M EUROPEANS

30% primary non-response rate for TNF biologics

50% acquire resistance for leading TNF biologics

Etiological Factors

Genetic Factors and Predisposition

Inflammation

NOX, iNOS, MPO

Oxidative Stress

NF-κB, others

Perpetual Mucosal Injury and Inflammation

Development of IBD

(team to research patient pop. in Japan and verify non-response rates)
Critical Unmet Need

NEC is a LEADING Cause of Mortality and Morbidity in Premature Infants

• From 2000-2011 deaths of extremely premature infants from other causes declined, but NEC related deaths increased
• No effective preventive therapies, current treatment is supportive
• Breast milk is efficacious but availability and quality is inconsistent
• Probiotics have some use (OUS) – with inconsistent evidence of benefit

Novel, Multi-Factor MOA Promotes Direct Healing

**NRG-4**

Naturally Occurring Peptide That Works with the Body to Restore Intestinal Homeostasis

1. **ANTI-INFLAMMATORY**
   - Induces apoptosis of M1 macrophages, protects against pathogen induced inflammatory injury

2. **PROTECTIVE**
   - Prevents intestinal cell death triggered by inflammatory cytokine, chemical, or pathogen insults

3. **RESTORATIVE**
   - Promotes survival of Paneth cells, maintaining the stem cells niche to regenerate the epithelium
ErbB4 Expression Is Increased in Disease States

NEC
- Tissues from patients with and without NEC stain for ErbB4 receptor
- Abundant brown stain along epithelium and crypts indicate presence of ErbB4 receptor in newborn intestine

Control

Crohn’s
- Representative crypts show nuclear staining in the epithelium of the Crohn’s tissue

Normal

IBD
NRG-4 Levels are Decreased in IBD

A & B. qPCR Analysis for NRG4 (A) and HRG-1β (B) gene expression was performed on TissueScan Crohn’s/colitis qPCR arrays. Relative mRNA levels were calculated using actin as reference. No change in expression was noted for the shared ErbB3/ErbB4 ligand HRG-1β.

C. Colonic homogenates from wild type controls (WT) or IL-10−/− mice were subjected to Western blot analysis for ErbB4, phospho-ErbB4 (P-ErbB4), and NRG4. UC: ulcerative colitis

Bernard, J.K. et al. (2012) Neuregulin-4 is a survival factor for colon epithelial cells both in culture and in vivo. J. Biol. Chem. 287 (47), 39850-39858.
Rebalancing the Levels of NRG-4 and ErbB4 to Prevent / Treat Disease

Pre-Clinical Studies Have Established That NRG-4 and ErbB4 Are Altered in GI Mucosa in Health and Disease

- **NO DISEASE**: Receptor and ligand levels are balanced.
- **DISEASED**: Receptor levels dramatically increase in epithelial cells, NRG-4 levels are lower in disease state.
- **REBALANCED**: NRG-4 is administered pharmacologically to prevent / treat disease.

**ErbB4 Receptor**

- Naturally found in the gut
- Plays an important role in gut homeostasis
- Induced by inflammation in pathologic state

**NRG-4 Ligand**

- Plays a natural protective role in the gut
- Binds exclusively to ErbB4
- Signals through the AKT pathway
- Human breast milk contains 159±34ng/mL* of NRG-4
- NRG-4 expression is decreased during active inflammation

* Mean ± SD
NRG-4 Plays a Natural Protective Role in the Gut

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<th>EXPERIMENTAL CONDITION</th>
<th>GI DISEASE RELEVANCE</th>
<th>NRG-4 PROTECTION</th>
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| Inflammatory Injury (TNF/IFNγ challenge) | • Intestinal inflammation  
• Colonic cell apoptosis                                                                     | ✓                |
| Chemical Injury (DSS colitis model)    | • Damaged mucosal barrier  
• Intestinal inflammation                                                                 | ✓                |
| Hypoxia Challenge (Formula Feeding/Hypoxia NEC* model) | • Immature gut development  
• Hypoxic injury  
• Damaged mucosal barrier                                                              | ✓                |
| Bacterial Injury (Dithiazone/Klebsiella Pneumonia NEC* model) | • Immature gut development  
• Compromised gut anti-microbial defenses  
• Bacterial colonization  
• Damaged mucosal barrier                                                                 | ✓                |

NRG-4 is effective against a broad range of insults including chemical, inflammatory and bacterial challenges

*NEC: necrotizing enterocolitis
NRG-4 Blocks Cytokine-induced Apoptosis *In Vivo* and Improves Experimental Colitis.

NRG-4 blocked apoptosis in the colons of mice induced by TNFα and IFNy. Co-injection of NRG-4 i.p. with TNF and IFNγ reduced cleaved caspase-3 on isolated epithelial cells from colons harvested 24 hours after the injection. Inhibition of apoptosis by NRG-4 was also demonstrated to be statistically significant in situ by reduced ISOL staining of fixed, paraffin-embedded colons.

Bernard, J.K. et al. (2012) Neuregulin-4 is a survival factor for colon epithelial cells both in culture and in vivo. J. Biol. Chem. 287 (47), 39850-39858.
NRG-4 Improves Outcome in IBD Rodent Model

Bernard, J.K. et al. (2012) Neuregulin-4 is a survival factor for colon epithelial cells both in culture and in vivo. J. Biol. Chem. 287 (47), 39850-39858.
NRG-4 Ameliorates Inflammation in IBD Rodent Model

Outcome in DSS treatment model:
IP injection of NRG-4 reversed weight-loss, ameliorated colon shortening and diarrhea, reduced macrophage numbers, and reduced levels of the macrophage-expressed pro-inflammatory cytokines TNFα, IL6, and IFNγ.

NRG-4 Activation of ErbB4 Induces Apoptosis of Pro-Inflammatory M1 Macrophages in Culture

NRG-4 Blocks Paneth Cell Loss and Pathogen-Induced GI Damage
Dithizone/Klebsiella Pneumoniae NEC Model

A. Ileums from 14-day-old mice subjected to D/K NEC, with or without NRG4, underwent staining by Alcian blue/periodic acidSchiff (AB/PAS) and immunohistochemical analysis for lysozyme to identify Paneth cells (arrowheads).

B. Paneth cells per crypt from five mice per condition (>50 crypts per mouse) were counted.

*P < 0.05, **P < 0.01.

NRG-4 Prevents Apoptosis in Immature Gut
Formula Feeding/Hypoxia NEC Model

Oral dosing of NRG-4 improved the histology and reduced apoptosis in the FFH NEC model in rat pups. Immunostaining for ErbB4 showed an increase in receptor expression in FFH versus dam-fed (DF) pups.

NRG-4 Safety Profile

NRG-4

- DOES NOT have tumor-promoting effects in an animal model of chronic gastrointestinal inflammation
- DOES NOT stimulate cell proliferation in several human colon cancer cell lines
- Unlike EGF, DOES NOT stimulate cell proliferation in rodent intestinal cell lines

Based on These Data, Oral NRG-4 Administration, That Is Expected to Have Minimal Systemic Exposure, Should Not Have Undesirable Mitogenic Effects
IBD
A Novel Topical / Oral Treatment That Directly Protects and Repairs the Mucosal Lining

First in Human Proof of Concept UC Enema Patients

Phase 2 IND study Commercial Formulation Oral (tablet/capsule)
Clinical Development Strategy - Co-Induction and Maintenance through Mucosal Healing

**Alternative to Immune Modulators**
Combination Induction Rx, Maintenance Rx to Control Flares

**Target Population(s)**

- Co-induction or Maintenance with ASA, displacing steroids (unwanted side effects)
- Maintenance or flare Rx in place of immune-modulators (6-MP, Azathioprine)
- Bridge or prior to existing IV Biologics (i.e. TNF, Integrins, JAK)

*Primary non-responders (30%); 50% acquire resistance to anti-TNF*

*BMJ 2017;357:j2505*
First in Human Proof of Concept

Safety

Distal UC Adults n=75 (to detect endoscopic response)

Topical Enema Administration

Efficacy: Endoscopic Response Rate
Multiple Benefits of Our Development Strategy

SHORTER timeline to value

SHORTER timeline to 1st in human safety and efficacy data

HISTOLOGIC EVIDENCE of healing

PROOF OF CONCEPT of direct gut mucosal activity, non-systemic

FASTER PROGRESS to a potential liquidity event at completion of initial human POC
Phase 1 ORAL

- Adult, healthy volunteers n = 25
- Safety
- Oral administration
- 4 weeks

Phase 2 Efficacy Design(s)

- Moderate-Severe disease, escalating Rx
- Steroid Sparing
- Dose escalation → 2 doses of NRG4
- Safety determinants
- Efficacy
- 12 weeks dosing
NRG-4 Development Timeline

Complete

YEAR 1

Preclinical Pharmacology Dev

Seed

YEAR 2

Pre-IND

AUS IRB

Human POC: $13M

Phase 1

UC POC

Phase 2

UC IND

YEAR 3

Through Clinical Phase 2:

YEAR 4

Human POC

UC Enema

CRO Clinical Study Management

GMP DS & DP

Bioanalytical Method Development

Enema & Oral Formulation Dev.

MCB Process Dev. & Demo Run

Eng. Run

UC POC Tox

GLP Tox

Seed

Human POC

UC POC

Human POC

UC Enema

UC POC

AUS IRB

Preclinical Pharmacology Dev

Pre-IND

Human POC: $13M

Through Clinical Phase 2:

CRO Clinical Study Management

GMP DS & DP

Bioanalytical Method Development

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Backup Slides
Distal UC- Topical Therapy (Enema)

- 60-80% of UC patients present as distal UC
- Rx of distal UC, targeting of drug to the distal colon is a priority
- Maintenance Rx – long-term toxicity and compliance with medications are key determinants
- 40% Proctitis- Proctosigmoiditis with mild-moderate disease → Not in Remission

ADDRESSABLE MARKET
- Approximately 700,000 patients in US suffer with UC
- 30% are diagnosed with left-sided UC

4. CDC - Epidemiology of the IBD - Inflammatory Bowel Disease 2017