Development and Commercialization Challenges with a Novel Anti-Infective Biofilm Technology

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HYBENX® Technology Development Challenges

• Disruptive Platform
• Simple
• Complex Paradigm: History of microbial disease
  – Clinical SOC for conventional microbiology
  – Antibiotics, disinfectants, cleanliness
  – Product complexity and regulatory expectations
  – Idiopathic disease
  – Global interconnectedness: more virulent and resistant strains
  – Biofilms
HYBENX® Technology Commercialization Challenges

• Established business knowledge is conservative: we know what works (NIH)
• Financial establishment
  – Industrial
  – Academic
• Reputational risk; personal and institutional
• Regulatory structure
• Legal liability risk
Lack of Significant Biofilm
“Normal” Biofilm Diversity
“Mature” Biofilm Development
Microbial Biofilm Cycle

“Normal”
Aerobic and facultative anaerobic commensal bacteria,
Diverse, Non-pathogenic,
*Healthy*

“Abnormal”
Anaerobic, pathogenic,
Antibiotic-resistant persister cells
*Inflammatory*
*(Periodontal Disease; Chronic Non-Healing Wounds, Etc.)*
Current Global View of Oral Microbial Biofilm

Overwhelming global evidence points to a changing infectious disease model where microbial agents and inflammatory mediators present in oral biofilm contribute to many chronic and acute diseases throughout the human body.


Current Therapeutic Approaches are Inadequate

Debridement is incomplete:
- Residual abnormal biofilm bacteria easily repopulate
- Inflammatory components not eliminated

Biofilm macromolecular microenvironment protects microbes and maintains inflammatory state:

- Antibiotic penetration incomplete
- Complex anaerobic biochemistry
- Accelerated horizontal gene transfer
- Persister cells increasing resistance
- Flawed “New” antibiotic development paradigm

A new molecular cleaning paradigm is needed.
EPIEN Medical’s HYBENX® Technology

A unique blend of common sulfonated phenolic acid constituents that have been safely used in global products as medical astringents, mucolytics, detergents, etc., since the early 1900s.
HYBENX: Molecular Desiccation

The Sulfate-Water Hydrogen Bonding Effect:
Localized Denaturation by Removal of Bound Water
Oral Mucosal Ulcers (Aphthae)

Mucosal Ulcer

Immediately post-HYBENX Application for 5 seconds

Hours post HYBENX Application

Week post-HYBENX Application
Microbial Biofilm Eradication Model (Innovotech)

**PSEUDOMONAS BIOFILM**

Untreated Control

HYBENX Treated

**CANDIDA BIOFILM**

Untreated Control

HYBENX Treated

**ASPERGILLUS BIOFILM**

Untreated Control

HYBENX Treated
Porcine and Human Skin Microbial Biofilm Eradication Models

University of Miami, Miller School of Medicine (S. Davis)

Porcine

*Acinetobacter baumannii*
*Methicillin-Resistant Staphylococcus aureus*
*Pseudomonas aeruginosa*

Human (cell culture)

*Trichophyton rubrum*
Oral Biofilm Evaluations – Live/Dead Confocal Full Depth Microscopy (Costerton – Lawrence)

UNTREATED CONTROL
Green = Live cells

HYBENX® TREATED
Red = Dead cells
USC Dental School Human Oral Biofilm SEM Studies

UNTREATED CONTROL – TOOTH BIOFILM
USC Dental School Human Oral Biofilm Studies

HYBENX TREATED; Not rinsed
Giorgio Lombardo, MD, “DDS”

Professor & Chair, Department of Periodontology, University of Verona
Effect of HYBENX® Oral Tissue Decontaminant on Periodontal Biofilm Microbes - DNA Analyses

16s PCR rDNA analysis

Samples taken from periodontal pockets before and after HYBENX rinse treatments

Contract laboratory assesses microbial identity and quantity
Oral Microbial DNA Probe Analyses

**Higher Risk**
- Aa = *Aggregatibacter actinomycetemcomitans*
- Pg = *Porphyromonas gingivalis*
- Tf = *Tannerella forsythia*
- Td = *Treponema denticola*

**Moderate Risk**
- Cr = *Campylobacter rectus*
- En = *Eubacterium nodatum*
- Fn = *Fusobacterium nucleatum/periodonticum*
- Pm = *Peptostreptococcus (Micromonas) micros*
- Pi = *Prevotella intermedia*

**Lower Risk**
- Cs = *Capnocytophaga sp. (gingivalis, ochracea, sputigena)*
- Ec = *Eikenella corrodens*
Baseline: Periodontal Pocket Microbial Composition Before HYBENX Treatment

### High Risk Pathogens
- **Aa**
- **Pg**
- **Tf**
- **Td**

### Moderate Risk Pathogens
- **En**
- **Fn**
- **Pi**
- **Cr**
- **Pm**
- **Ec**

### Low Risk Pathogens
- **Cs**
Periodontal Pocket Microbial Composition after SRP and HYBENX Treatment

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Effect of HYBENX® Oral Tissue Decontaminant on Periodontal Inflammatory Markers

Inflammatory modulators are molecular surrogate markers of chronic inflammatory disease

Primary periodontal markers appear to be MMP8 along with IL-1β, IL-6, and TNF-alpha

Assayed effect of HYBENX Solution on the levels of these inflammatory markers in patient periodontal quadrants
Molecular Cleansing of Periodontal Inflammatory Markers by HYBENX-Immunoassay Results

Figure 2. Evaluation of Biomarkers in Paper Point Samples Collected Pre and Post HYBENX Irrigation Treatment

- **MMP-8**
  - Pre: C1 > C2
  - Post: C1 = C2

- **IL-1β**
  - Pre: C1 > C2
  - Post: C1 = C2

- **IL-6**
  - Pre: C1
  - Post: C1

- **TNF-α**
  - Pre: C1
  - Post: C1

**NOTES**

- **Collection Set 1 (C1):** Pooled paper points eluted with 150 μL of PBS, assayed at a 1:2 dilution.
- **Collection Set 2 (C2):** Pooled paper points eluted with 50 μL of PBS, assayed at a 1:6 dilution (Due to the 1:6 dilution, IL-6 and TNF-α were not detectable.)
- TNF-α Post value presented a result < MDD of 2.40 pg/mL. MDD value graphed for demonstration purpose. (MDD=mean detectable dose)
A Topical Desiccant Agent In Association With Ultrasonic Debridement In The Initial Treatment Of Chronic Periodontitis: A Clinical And Microbiological Study.

G Lombardo, C Signoretto, G Corrocher, A Pardo, J Pighi, A Rovera, F Caccuri, and PF Nocini. New Microbiologica 38:393-407. 2015

Summary

This controlled randomized pilot clinical trial demonstrated that debridement accompanied by the use of HYBENX® Oral Tissue Decontaminant resulted in clinically superior patient outcomes as assessed with both microbial and clinical parameters.
1st Annual Conference

ELIMINATION OF BACTERIAL BIOFILM: A NEW APPROACH FOR THE TREATMENT OF PERIODONTITIS AND PERI-IMPLANTITIS: FROM RESEARCH TO CLINICAL PRACTICE

Florence, Italy
16 May 2015

Scientific Coordinator
Prof. Giovan Paolo Pini Prato

Session Coordinators
Dr. Pierpaolo Cortellini and Dr. Nicola M Sforza

Speakers
James W Bracke, PhD
Prof. Francesco Carinci, MD
Dr. Dorina Lauritano, MD
Dr. Zdenek Jansky, MD
Dr. Stefan Neumeyer, MD
Prof. Giovan Paolo Pini Prato, MD
General HYBENX Oral Cleaning Regimen

• Apply HYBENX Solution for approximately 10 - 20 seconds; rinse/aspirate—loosens plaque biofilm, reduces subsequent pain and bleeding
• Perform conventional SRP/UD
• Second HYBENX treatment: cleans residual molecular debris and “seals” tissue surface
Regulatory Challenges

- Old definitions of drug vs. device vs. combination products
- Chemical action vs. metabolic process: desiccation?
- Contact under one minute; Not absorbed; no residue; focal
- Extensive safety file
- 2003: Formal US, Canada, and EU HYBENX Product Registration activity
- 2005: Canada Broad Oral Class I Medical Device
- 2005/6: EU Broad Oral Class I Medical Device
- US: Device section; OCP; device section; legal resolution
- 2013: EPIEN Root Canal Cleanser 510(k) Oral Device
- To date:
  - 8 million oral units sold with 200+ complaints
  - US – Future development activity?
Future Chronic Disease Clinical Targets: Therapy Beyond the Oral Cavity?

• Non-healing Chronic Wounds
  – Dr. Marcus Gitterle
  – CHRISTUS Hospital System, San Antonio TX  USA
  – 50+ patients
    • NHCW = 5-15 months old (Va, Di, De, SSI)
    • Ten-second therapeutic application
    • “Cools” down the hot spot
    • Complete re-granulation and preliminary epithelialization within four weeks

• Additional independent anecdotal clinical reports
• University of Sapienza
Chronic Venous Stasis Ulcer
HYBENX® Oral Tissue Decontaminant Solution

www.hybenx.it
Simplicity is the ultimate sophistication...

Leonardo da Vinci

The irony of the world is that it wants to simplify complexity and complicate simplicity...

Vikrmn