Vaginal Microbiota

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Only a minority of women have a ‘normal’ lactobacillus dominated vaginal microbiota.

<table>
<thead>
<tr>
<th>Type</th>
<th>% of U.S. Women</th>
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<tbody>
<tr>
<td>Normal</td>
<td>~38%</td>
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<tr>
<td>BV</td>
<td>~29%</td>
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<tr>
<td>Intermediate</td>
<td>~33%</td>
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Uterine peristalsis actively transports microbiota and pathogens in the vagina to the entire upper tract.

**Scintigraphy (Kadanali ‘00)**

Uterine peristalsis pumps fluids from the vagina up and into the fallopian tube on the side that ovulates.

**MRI (Barnhart ‘01)**

Microbicide gel in the vagina ascends into the endocervical canal (arrow).

**Ultrasound (Parsons ‘04)**

Semen is transported into the uterus at all stages of the menstrual cycle.
Bacterial vaginosis is recurrent

Lactobacillus microflora

Data from R. Brotman

Composition of vaginal microbiota
The pH of the vagina correlates inversely with the concentration of lactic acid when Lactobacilli dominate the vaginal microbiota, Nugent Scores <3.
Lactic acid is a potent microbicide against BV-associated bacteria.
Lactic acid potently inactivates viruses, bacteria, and protozoa:

HIV, HSV, C.trachomatis, and T. vaginalis
   Aldunate M, Tyssen D, Johnson A, Zakir T, Sonza S, Moench T, Cone R, Tachedjian G. Vaginal concentrations of lactic acid potently inactivate HIV.

Bacteria associated with poor birth outcomes
   O’Hanlon, in preparation

Lactic acid has anti-inflammatory effects on cytokines secreted by vaginal epithelium in contrast to the inflammatory cytokines stimulated by BV.
All four diamines produced by BV bacteria inactivate Lactobacilli, and inactivate *L. crispatus* more potently than *L. iners*.

Lihan Lai, Masters Thesis, JHU 2010
Treatment for BV with oral probiotic *L. rhamnosus & L reuteri* and tinidazole. Patients received either the probiotic or placebo for 28 days starting on the first day of tinidazole use.

Changes in vaginal microbiota following antimicrobial and probiotic therapy. Macklaim ....

Gregor Reid. Canadian Research & Development Centre for Microbiome and Probiotics, London, Ont. Microbial Ecology in Health & Disease 2015, 26: 27799
Vaginal lactobacilli are coated, with high variability, with secreted antibodies.

Fluorescent Intensity

Nugent Score < 3

Intrinsic Fluorescence
BV bacteria with much higher IgA coverage than vaginal lactobacilli
BV bacteria with higher IgG coverage than vaginal lactobacilli
### Clinical Pipeline

<table>
<thead>
<tr>
<th></th>
<th>Pre-Clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tbody>
<tr>
<td>LACTIN-V</td>
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<tr>
<td>Bacterial vaginosis</td>
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<tr>
<td>Recurrent urinary tract infections</td>
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<tr>
<td>Candida (yeast) infections</td>
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<td>CBM588</td>
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<tr>
<td><em>Clostridium difficile</em> associated diseases</td>
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<tr>
<td>MucoCept Platform</td>
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<tr>
<td>HIV (grant funded)</td>
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<tr>
<td>HSV, chlamydia, other STDs</td>
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A layer of vaginal epithelial cells is shed every ~6 hours.

Wang Y-Y & Cone, GRC, 2013
Rakoff et al, AJOG, 1944
Rebiotix was founded with $5M in 2011.

In 2012, a Pre-Investigational New Drug (IND) meeting with FDA for RBX2660 was held.

In 2013, FDA IND was granted and Fast Track designation was granted. The PUNCH CD phase 2 trial was enrolled for RBX2660 to treat recurrent *Clostridium difficile*.

In 2014, a $25M Series B round fundraising was completed. FDA Orphan Drug designation was granted. Results of PUNCH CD were announced. PUNCH CD 2 (phase 2b) trial was initiated. Development of oral formulation, RBX7455, was started.

In 2015, PUNCH CD 2 enrollment for RBX2660 was completed. FDA Breakthrough Status was granted for RBX2660. Oral formulation Drug Master File (DMF) was filed with FDA.