The next generation of probiotics

Microbial ecosystem therapeutics

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Better ecosystem, better health
Only very few microbes are pathogens
In fact, human health *depends* on microbiota health

We are the vessels for our microbial passengers
Maintaining the equilibrium

High diversity of species:
- Healthy ecosystem
- Balance
- Functional redundancy
- Resistance to disease

Low diversity of species:
- Sick ecosystem
- Imbalance
- Functional disability
- Susceptibility to disease
Gut bug diversity

• ~500 different bacterial species in an average gut
  – Collectively do as much metabolic ‘work’ as the average liver
• We all have a unique genome, unique fingerprints, unique iris patterns…
• …and a unique profile of gut microbes
What do our gut microbes do for us?

- Help to digest otherwise indigestible foods
- Provide colonization resistance
- Educate the immune system
- Make molecules that are beneficial (even critical) to health

http://www.fireboxmedia.com/illustration/
And what do we do to them?

Antibiotic use

Poor, Western style diet

Excessive sanitation

**Missing microbiota hypothesis**
- We are disturbing proper colonization of our bodies with microbes
- The effects may compound over generations

Blaser & Falkow 2009
• Several studies have shown:
  – Gut microbiota changes significantly with antibiotic use
  – Takes a long time afterwards to return to baseline
  – Sometimes does not return to baseline at all
  – Repeated ‘hits’ cause vast changes from which the ecosystem does not recover

Our approach to fixing a damaged gut ecosystem…

• Isolation of a 33-strain, 25 species microbial ecosystem derived from a single, very healthy donor
  – Test for ecosystem stability *in vitro*

• Copies the fecal transplant approach to treatment of gut disease
  – But is safer, more acceptable, more stable and completely defined

“RePOOPulate”
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- Acidaminococcus intestinalis
- Bacteroides ovatus
- Bifidobacterium adolescentis (x2)
- Bifidobacterium longum (x2)
- Collinsella aerofasciens
- Dorea longicatena (x2)
- Escherichia coli
- Eubacterium eligens
- Eubacterium limosum
- Eubacterium rectale (x4)
- Eubacterium ventriosum
- Faecalibacterium prausnitzii
- Lactobacillus casei
- Lactobacillus paracasei
- Parabacteroides distasonis
- Raoultella sp.
- Roseburia faecalis
- Roseburia intestinalis
- Ruminococcus torques (x2)
- Streptococcus mitis
- Likely novel species (x5)
- Likely novel genus & species (x1)

Not just the usual probiotic subjects!
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RePOOPulate proof-of-principle trial

- 2 elderly ladies with severe, recurrent *C. diff* infections were treated (April and June 2011)
- RePOOPulate made fresh at Guelph, driven to KGH, and administered via colonoscopy
  - 1 dose, 100mLs
- Both patients recovered within 2 days and have remained *C. diff*-free ever since (despite numerous subsequent antibiotic exposures)

**Scientific American™**

Fake Feces To Treat Deadly Disease: Scientists Find They Can Just Make Sh*t Up

By Christie Wilcox |
Microbes work better in teams

- Probiotic strains vs. probiotic ecosystems

Probiotic strains – single or few species acting alone

Microbial synergy: bugs support each other to create an overall larger benefit
Next steps

• Need to move beyond traditional probiotics
  – New probiotic species are hard to culture \textit{(but not impossible!)}

• Need for beneficial microbes to work as a group in an ecosystem
  – Sticking point – regulatory issues
  – E.g. growth and safety parameters not yet measured
  – Should not be an excuse not to develop these further