PERSONALIZING PREBIOTIC REGIMENS for ASTRONAUTS

LAWRENCE DAVID
Assistant Professor, Molecular Genetics & Microbiology
Associate Director, Duke Microbiome Center
Duke University
• All animals are colonized by microbial communities
• All animals are colonized by microbial communities

• In humans:
  • \(~100\) trillion bacteria colonize epithelial surfaces
  • 100 billion bacteria per gram of fecal matter in the colon
**The New York Times**

**Health**

**Gut Bacteria From Thin Humans Can Slim Mice Down**

By GINA KOLATA
Published: September 5, 2013

**Time**

**The Bacteria That May One Day Cure Food Allergies**

Mandy Oaklander @mandy oaklander
Aug. 25, 2014

**ScienTific American**

**Gut Bacteria May Play a Role in Autism**

Evidence is mounting that intestinal microbes exacerbate or perhaps even cause some of autism’s symptoms

Aug 14, 2014 | By Melinda Wenner Moyer

**The Telegraph**

**Drinking milk could be behind rise in bowel disease**

Diets rich in milk could be behind the growth in cases of inflammatory bowel disease because they fill our guts with "bad bacteria", a study on mice suggests.

**The Atlantic**

**When Feces Is the Best Medicine**
GUT MICROBIOME IS DYNAMIC

David et al., *Genome Biol* 2014
DIET CAN BE A WAY TO MANIPULATE
DIET CAN BE A WAY TO MANIPULATE

Microbiota Dissimilarity (JSD)

Plant-based diet

Baseline Washout

Day

1 3 5 7 9 11 13 15

80% 60% 40% 20%

% samples

David et al., Nature 2014
DIET CAN BE A WAY TO MANIPULATE

Microbiota Dissimilarity (JSD)

<table>
<thead>
<tr>
<th>Plant-based diet</th>
<th>Animal-based diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Baseline</td>
</tr>
<tr>
<td>Washout</td>
<td>Washout</td>
</tr>
</tbody>
</table>

Day

Fat intake (Calorie fraction)

Fiber intake (Calorie fraction)

* * * *

David et al., Nature 2014
PREBIOTICS

- Prebiotics are *indigestible dietary carbohydrates* known to stimulate gut microbiota
Prebiotics are **indigestible dietary carbohydrates** known to stimulate gut microbiota.

### Subject A Gut

<table>
<thead>
<tr>
<th>Body Site</th>
<th>Lag (days)</th>
<th>Host factor</th>
<th>Representative OTUs (#)</th>
<th>( \rho )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool:Hardness</td>
<td>0</td>
<td>Eggerthella/Clostridium(11)</td>
<td>-0.30</td>
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<tr>
<td>Nutrition:Fiber</td>
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<tr>
<td>Food:OrangeJuice</td>
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<td>Food:Yogurt</td>
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<tr>
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David et al., *Genome Biology* 2014
PREBIOTICS

- Prebiotics are **indigestible dietary carbohydrates** known to stimulate gut microbiota

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David et al., Genome Biology 2014
• Prebiotics are *indigestible dietary carbohydrates* known to stimulate gut microbiota

• Of interest because gut microbial fermentation leads to short-chain fatty acids like **butyrate**, a primary energy source for colonic epithelial cells
Prebiotics are indigestible dietary carbohydrates known to stimulate gut microbiota.

Of interest because gut microbial fermentation leads to short-chain fatty acids like butyrate, a primary energy source for colonic epithelial cells.

Also of relevance to spaceflight because shelf-stable and tend to originate in plants.
How can prebiotic regimens be rationally designed?

- Dozens of dietary fiber species exist

<table>
<thead>
<tr>
<th>Prebiotics: Oligo- and Polysaccharides</th>
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<tbody>
<tr>
<td>Amylopectin (corn)</td>
</tr>
<tr>
<td>Amylopectin (potato)</td>
</tr>
<tr>
<td>Arabinan</td>
</tr>
<tr>
<td>Arabinogalactan</td>
</tr>
<tr>
<td>Arabinoxyylan (wheat)</td>
</tr>
<tr>
<td>Cellobiose</td>
</tr>
<tr>
<td>Chitin</td>
</tr>
<tr>
<td>Chondroitin sulfate</td>
</tr>
<tr>
<td>Dextran</td>
</tr>
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</table>
HOW CAN PREBIOTIC REGIMENS BE RATIONALLY DESIGNED?

- **Dozens** of dietary fiber species exist
- Each may **vary in effect**

<table>
<thead>
<tr>
<th>Group</th>
<th>Butyrate Before</th>
<th>Butyrate During</th>
<th>Change (%)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Accessible starch</td>
<td>13 ± 6.1</td>
<td>15 ± 8.3</td>
<td>+13</td>
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<tr>
<td>(n = 39)</td>
<td>(n = 39)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hi-Maize</td>
<td>9.3 ± 4.1</td>
<td>9.7 ± 5.6</td>
<td>+5</td>
<td>0.81</td>
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<tr>
<td>(n = 43)</td>
<td>(n = 43)</td>
<td></td>
<td></td>
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<tr>
<td>Potato</td>
<td>13 ± 6.0</td>
<td>16 ± 7.5</td>
<td>+29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n = 43)</td>
<td>(n = 43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inulin</td>
<td>11 ± 6.0</td>
<td>13 ± 7.0</td>
<td>+17</td>
<td>0.14</td>
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<tr>
<td>(n = 49)</td>
<td>(n = 49)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1

Baxter et al., *mBio* 2019
How can prebiotic regimens be rationally designed?

- **Dozens** of dietary fiber species exist
- Each may **vary in effect**
- **Individuals also vary** in response

**Fig. 2** Median butyrate concentrations for each individual before (triangles) and during consumption of RS (circles). Dotted and dashed lines denote the median values for butyrate before and during RS, respectively, for the entire study population.
HOW CAN PREBIOTIC REGIMENS BE RATIONALLY DESIGNED?

• Dozens of dietary fiber species exist
• Each may vary in effect
• Individuals also vary in response

How do we avoid provisioning astronauts with prebiotics that don’t work?
Answer three questions for astronauts:

• Which prebiotics should they take?
• Who should take them?
• And, when?
GOALS OF OUR WORK

Answer three questions for astronauts:

- Which prebiotics should they take?
- Who should take them?
- And, when?
CHALLENGES TO SCREENING PREBIOTICS

- Potentially a large number of prebiotics to screen
- Human studies can be logistically demanding
- *In vivo* physiological variation (e.g. SCFA absorption) may mask microbial response
A SIMPLE HOST-FREE PREBIOTIC ASSAY

**PUMP**: Prebiotic Utilization and Metabolite Production

1. Stool is self-collected and frozen. Transported on ice to laboratory
2. Thawed stool is weighed, and appropriate volume of PBS is added
3. Stool and PBS mixed, slurry filtered through mesh to remove particulates
4. Stool slurry and prebiotic solution are added to 24-well plates
5. Plates are incubated at 37 degrees in an anaerobic chamber for 24 hours
6. SCFA concentration is measured using a gas chromatograph FID

Holmes et al., *mBio* 2020
OBSERVED SIGNIFICANT VARIATION BETWEEN PREBIOTICS

We observed significant variation between prebiotics and metabolism study. We found all 17 individuals demonstrated a net gain of SCFAs relative to the control in at least one prebiotic treatment, which led us to conclude that all tested cultures were viable and metabolically active (Fig. 3).

Donor and prebiotic both impact SCFA production in vitro. We next tested the hypothesis that different prebiotics equally promote the production of SCFAs by in vitro SCFA production by prebiotic (A), donor (B), and individually (C). In a two-way ANOVA of the effects of "donor" and "prebiotic" on "SCFA concentration/control," "donor," "prebiotic," and their interaction were all statistically significant (P/H11021 < 0.0001, P/H11021 < 0.0001, and P/H11021 < 0.0001, respectively). Shown is the total SCFA concentration of an in vitro culture after 24 h of anaerobic incubation, divided by the SCFA concentration of the corresponding prebiotic-free control culture, for each of five prebiotic growth conditions across 17 donors (black dots). Gray diamonds are means, and gray bars are standard deviations. (Absolute SCFA concentrations are depicted in Fig. S3.)

Gut Microbial SCFA Production in Pediatric Obesity

July/August 2020 Volume 11 Issue 4 e00914-20
mbio.asm.org

Holmes et al., mBio 2020

n=17 stool donors
P < 0.0001, two-way ANOVA
We found all 17 individuals demonstrated a net gain of SCFAs relative to the control in at least one prebiotic treatment, which led us to conclude that all tested cultures were viable and metabolically active (Fig. 3).

Donor and prebiotic both impact SCFA production in vitro. We next tested the hypothesis that different prebiotics equally promote the production of SCFAs by

**FIG 3**

In vitro SCFA production by prebiotic (A), donor (B), and individually (C). In a two-way ANOVA of the effects of "donor" and "prebiotic" on "SCFA concentration/control," "donor," "prebiotic," and their interaction were all statistically significant ($P < 0.0001$, $P < 0.0001$, and $P < 0.0001$, respectively). Shown is the total SCFA concentration of an in vitro culture after 24 h of anaerobic incubation, divided by the SCFA concentration of the corresponding prebiotic-free control culture, for each of five prebiotic growth conditions across 17 donors (black dots). Gray diamonds are means, and gray bars are standard deviations. (Absolute SCFA concentrations are depicted in Fig. S3.)

Holmes et al., *mBio* 2020
GOALS OF OUR WORK

Answer three questions for astronauts:

• Which prebiotics should they take?
• **Who** should take them?
• And, when?
HOW CAN WE STUDY INDIVIDUAL VARIATION?

Need *lots* of cultures:

- Each individual estimated to harbor *hundreds of unique* gut bacterial strains
HOW CAN WE STUDY INDIVIDUAL VARIATION?

Need lots of cultures:

- Each individual estimated to harbor hundreds of unique gut bacterial strains
- Millions of colonies needed to match sensitivity of DNA sequencing

Petri dishes to capture 90% of gut bacterial species
HOW CAN WE STUDY INDIVIDUAL VARIATION?

Need *lots* of cultures:

- Each individual estimated to harbor **hundreds of unique** gut bacterial strains
- **Millions of colonies** needed to match sensitivity of DNA sequencing

*Culture can be* **hard to scale:**
- Manual isolation can be **tedious** and **time-consuming**
HOW CAN WE STUDY INDIVIDUAL VARIATION?

Need **lots** of cultures:

- Each individual estimated to harbor **hundreds of unique** gut bacterial strains
- **Millions of colonies** needed to match sensitivity of DNA sequencing

Culture can be **hard to scale**:

- Manual isolation can be **tedious** and **time-consuming**
- Automation may require **expensive** and/or **bulky** robotics that need to be enclosed anaerobically
MICROFLUIDIC BACTERIAL CULTURE

Rachael Bloom
MICROFLUIDIC BACTERIAL CULTURE

Oil

Emulsion droplet

Isolated gut microbes

Media
MICROFLUIDIC BACTERIAL CULTURE

Can generate millions in minutes
APPLY TOWARDS
PREBIOTIC UTILIZATION

Metabolize carbon source of interest?

Isolate with sole carbon source

Max Villa
Figure 2. A prebiotic utilization screen based on the MicDrop platform.

(A) Schematic of MicDrop prebiotic assay. (B) Droplet monoculture growth of B. thetaiotaomicron in microfluidic droplets measured by qPCR. (C) Results of 96-well plate growth of gut bacterial isolates across 11 carbohydrates. (D) ROC curve of MicDrop assay results at different growth threshold cut-offs using (C) as a reference. The black dot indicates the growth threshold that maximizes the true positive rate while minimizing the false positive rate, depicted in (E). (F) Correlation between two different MicDrop sessions (each carried out in triplicate) on the same frozen fecal sample and five different carbohydrates. Points indicate median growth of different SVs across each experimental session.

APPLY TOWARDS
PREBIOTIC UTILIZATION

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<th>Metabolize carbon source of interest?</th>
<th>Isolate with sole carbon source</th>
<th>Growth restricted to microbes that utilize carbon source</th>
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Max Villa
APPLY TOWARDS
PREBIOTIC UTILIZATION
APPLY TOWARDS
PREBIOTIC UTILIZATION

Phylum
GOS
Glucose
Inulin
Dextrin
Xylan

Subject-Strain

Subject sequence variant

Firmicutes
Actinobacteria
Bacteroidetes
Proteobacteria

Phylum
Participant
EVERYONE HOSTS PREBIOTIC UTILIZERS

![Graph showing the number of taxa that grow on prebiotic substrates for different subjects. The x-axis represents the number of taxa, and the y-axis represents the subjects (A to I). The graph uses different colors to indicate the prebiotic substrates: Dextrin (light blue), Inulin (green), Xylan (pink), GOS (blue), and Glucose (brown).]
EVERYONE HOSTS PREBIOTIC UTILIZERS

But, people vary in abundance of utilizers across prebiotics

Villa*, Bloom*, et al., mSystems 2020
EVERYONE
HOSTS PREBIOTIC UTILIZERS

But, people vary in abundance of utilizers across prebiotics

Let’s start testing in people…

Villa*, Bloom*, et al., mSystems 2020
STUDY GOAL

• Test the hypothesis that individuals will vary in prebiotic metabolic potential, regardless of prebiotic
STUDY GOAL

• Test the hypothesis that individuals will vary in prebiotic metabolic potential, regardless of prebiotic

• Requires a unique study design where all individuals consume the same battery of prebiotics
CHoosing the OptiMal Prebiotic (CHOMP)

Randomize

Pre A | Pre A | Pre A
Pre B | Pre B | Pre B
Pre C | Pre C | Pre C
Pre A | Pre A | Pre A
Pre B | Pre B | Pre B
Pre C | Pre C | Pre C

Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6
Baseline | Intervention | Washout | Interv. | Washout | Intervention

Pre A: Inulin
Pre B: Dextrin
Pre C: Galactooligosaccharides

$n = 28$ healthy volunteers completed

ClinicalTrials.gov ID: NCT03595306

Holmes, et al., In prep
AGAIN, SIGNIFICANT VARIATION BETWEEN PREBIOTICS
IMPORTANTLY, INDIVIDUAL VARIATION CORRELATED ACROSS PREBIOTICS
WHAT DRIVES INDIVIDUAL VARIATION?
WHAT DRIVES INDIVIDUAL VARIATION?

![Graph showing the relationship between habitual dietary fiber consumption and average Δ% butyrate during intervention. The graph includes a scatter plot with a line of best fit, indicating a negative correlation. The p-value is 0.032, and the correlation coefficient (rho) is -0.43.]
WHAT DRIVES INDIVIDUAL VARIATION?

Can recent fiber intake affect prebiotic response?

Graph: Scatter plot showing the relationship between habitual dietary fiber consumption and Δ%Butyrate during intense exercise. The line of best fit indicates a negative correlation, with $p = 0.032$ and $\rho = -0.43$. The x-axis represents habitual dietary fiber consumption (g/Kcal) ranging from 0.00 to 0.03, and the y-axis represents Δ%Butyrate ranging from -0.02 to 0.00.
Answer three questions for astronauts:

- Which prebiotics should they take?
- Who should take them?
- And, when?
Exposure to prior doses of a prebiotic will affect microbiota response over time
TEST USING AN ARTIFICIAL GUT

Silverman, Durand, et al, Microbiome 2018
TEST USING AN ARTIFICIAL GUT

Minimum pH

6.9
6.8
6.7
6.6
6.5
6.4

no dose

NS

Jeff Letourneau
TEST USING AN ARTIFICIAL GUT

Inulin dose

Jeff Letourneau
TEST USING AN ARTIFICIAL GUT

Inulin dose

Jeff Letourneau
TEST USING AN ARTIFICIAL GUT

Jeff Letourneau
IS A SINGLE DOSE SUFFICIENT IN PEOPLE?

- Week 1: Baseline
  - T: Time (days)
  - F: Samples

- Week 2: Treatment
  - T: Time (days)
  - F: Samples

- Week 3: Followup
  - T: Time (days)
  - F: Samples

**Placebo group (n=8)**
- 9g maltodextrin
  - 2x/day

**Prebiotic group (n=8)**
- 9g inulin
  - 2x/day

\[ n = 40 \text{ healthy volunteers} \]
Within 6 hrs of prebiotic exposure, human gut bacteria **activate** polysaccharide utilization loci.
SUMMARY
SUMMARY

- Prebiotics vary in effect on gut microbiota
SUMMARY

• Prebiotics vary in effect on gut microbiota

• But, stronger individual variation in response
Prebiotics vary in effect on gut microbiota

But, stronger individual variation in response

Variation can be linked to gut microbial function, which in turn is linked to prior diet
SUMMARY

- **Prebiotics vary** in effect on gut microbiota
- But, **stronger individual variation** in response
- Variation can be **linked to gut microbial function**, which in turn is **linked to prior diet**
- Even **initial exposure** to prebiotics will **alter response to subsequent doses**
VISION FOR ASTRONAUTS

Three questions:
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Three questions:

1. Which prebiotics should they take?
VISION FOR ASTRONAUTS

Three questions:

1. **Which prebiotics** should they take?
   - Might **not matter** too much.
VISION FOR ASTRONAUTS

Three questions:

1. **Which prebiotics** should they take?
   - Might **not matter** too much.

2. **Who** should take them?
VISION FOR ASTRONAUTS

Three questions:

1. **Which prebiotics** should they take?
   - Might **not matter** too much.

2. **Who** should take them?
   - **Greatest benefit** among those who normally eat the least fiber
VISION FOR ASTRONAUTS

Three questions:

1. **Which prebiotics** should they take?
   - Might *not matter* too much.

2. **Who** should take them?
   - **Greatest benefit** among those who *normally eat the least fiber*

3. And, **when**?
VISION FOR ASTRONAUTS

Three questions:

1. Which prebiotics should they take?
   • Might not matter too much.

2. Who should take them?
   • Greatest benefit among those who normally eat the least fiber

3. And, when?
   • Poor responders may start shortly before spaceflight
What are the effects of prebiotics on cognition and mental performance?
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