Group 2

Prebiotics and oligosaccharides in the gut:

- Who (is enriched)?
- What (is the effect)?
- Where (do these effects occur)?
- How (are these effects manifested)?

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Janina Krumbeck
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How do you get to the National Academy of Science?

A. Be recognized for their distinguished and continuing achievements in original research, marked by excellence in science.

B. Be nominated, followed by an extensive and careful vetting process that results in a final ballot at the Academy's annual meeting in April each year.

C. Take the slowest damn bus in North America.

Prebiotics and oligosaccharides in the gut:

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PERSPECTIVES

OPINION

Towards a more comprehensive concept for prebiotics

Laure B. Bindels, Nathalie M. Delzenne, Patrice D. Cani and Jens Walter

NATURE REVIEWS | GASTROENTEROLOGY & HEPATOLOGY

Abstract | The essential role of the gut microbiota for health has generated tremendous interest in modulating its composition and metabolic function. One of these strategies is prebiotics, which typically refer to selectively fermented nondigestible food ingredients or substances that specifically support the growth and/or activity of health-promoting bacteria that colonize the gastrointestinal tract. In this Perspective, we argue that advances in our understanding of diet–microbiome–host interactions challenge important aspects of the current concept of prebiotics, and especially the requirement for effects to be 'selective' or 'specific'. We propose to revise this concept in an effort to shift the focus towards ecological and functional features of the microbiota more likely to be relevant for host physiology. This revision would provide a more rational basis for the identification of prebiotic compounds, and a framework by which the therapeutic potential of modulating the gut microbiota could be more fully materialized.

“In this Perspective, we argue that advances in our understanding of diet–microbiome–host interactions challenge important aspects of the current concept of prebiotics, and especially the requirement for effects to be ‘selective’ or ‘specific’.

We propose to revise this concept in an effort to shift the focus towards ecological and functional features of the microbiota more likely to be relevant for host physiology.

This revision would provide a more rational basis for the identification of prebiotic compounds, and a framework by which the therapeutic potential of modulating the gut microbiota could be more fully materialized.”

1995

A non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health

Gibson and Roberfroid,

2007

A prebiotic is a non-viable food component that confers a health benefit on the host associated with modulation of the microbiota

FAO Technical Report November 2007

2008

A prebiotic is a non-viable food component, ingredient or supplement that selectively modulates the microbiota of the digestive ecosystems, thus conferring benefits upon host well-being and health

ILSI Expert Group on the Working Definition of Prebiotics

2010

A dietary prebiotic is a **selectively** fermented ingredient that results in **specific** changes, in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health

ISAPP, IFIS Functional Foods Bulletin

Main arguments concern the requirement of selectivity and specificity

- good vs. evil, healthy vs unhealthy is an out-dated concept, depends on condition or disease
- current knowledge does not allow a reliable differentiation of beneficial and detrimental members within the gut microbiota
- the key metabolic benefits assigned to prebiotics do not require a “selective” fermentation, i.e., short chain fatty acids are produced by many bacteria, so why is selectivity necessary
- modern community-wide molecular approaches have revealed that even the established prebiotics are not as specific as previously assumed.

Question for Group 2 to consider:

Is the current definition of “prebiotics” adequate or should ISAPP convene a consensus panel to consider redefining "prebiotics”?

CONSENSUS STATEMENTS

OPEN

EXPERT CONSENSUS DOCUMENT

The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic

Colin Hill, Francisco Guarner, Gregor Reid, Glenn R. Gibson, Daniel J. Merenstein, Bruno Pot, Lorenzo Morelli, Roberto Berni Canani, Harry J. Flint, Seppo Salminen, Philip C. Calder and Mary Ellen Sanders

Abstract | An expert panel was convened in October 2013 by the International Scientific Association for Probiotics and Prebiotics (ISAPP) to discuss the field of probiotics. It is now 13 years since the definition of probiotics and 12 years after guidelines were published for regulators, scientists and industry by the Food and Agriculture Organization of the United Nations and the WHO (FAO/WHO). The FAO/WHO definition of a probiotic—“live microorganisms which when administered in adequate amounts confer a health benefit on the host”—was reinforced as relevant and sufficiently accommodating for current and anticipated applications. However, inconsistencies between the FAO/WHO Expert Consultation Report and the FAO/WHO Guidelines were clarified to take into account advances in science and applications. A more precise use of the term ‘probiotic’ will be useful to guide clinicians and consumers in differentiating the diverse products on the market. This document represents the conclusions of the ISAPP consensus meeting on the appropriate use and scope of the term probiotic.

506 | AUGUST 2014 | VOLUME 11

Group 2 was not persuaded that there was a need ***at this time*** to convene such a panel

Rather, the Group suggests ISAPP focus on other priorities:

- Research on mechanism of action
- Define/clarify terms used in the present definition
- Target larger number of outcomes from use of prebiotics
- Study prebiotic activity outside the gut.
- Prebiotic function - structure interaction studies needed.
- If the goal is to educate consumers, current definition is adequate

Prebiotics and oligosaccharides in the gut:

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1. Who is enriched?

- Enrichment of bifidobacteria and lactobacilli is well established, but what about other members of the microbiota?

Who cares? Does it matter? Functions are more relevant.

Enriching for a population is a means to an end.

Of course, mechanisms are important and necessary.

- Does the host microbiome predict or influence which members are enriched or affected by prebiotics?

Infant data would suggest so

Responders/non-responder data would suggest so

Data suggest considerable individual responses

- Do different prebiotics influence different gut members?

Prebiotics and fermentable carbohydrates/fibers have a large influence on the microbiota, but the effects are not easily assessed.

2. What and where is the effect?

- What role do other dietary carbohydrates (i.e., apart from GOS, FOS, inulin) have on the gut microbiota (such as plant fibers, starch, mucins, glucans, EPS, milk oligosaccharides)

This is the focus of multiple labs; may provide the next generation of prebiotics

- What is the impact of cross-feeding?

Cross-feeding is critically important, for better or worse, but is difficult to quantify or predict, especially *in vivo*

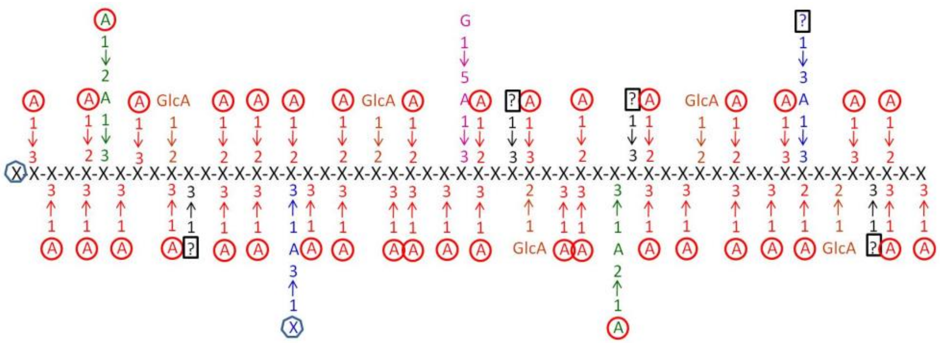
- What is the importance of location?

There are luminal and epithelial effects, as well as mucin adhesive effects, but much more effort is needed

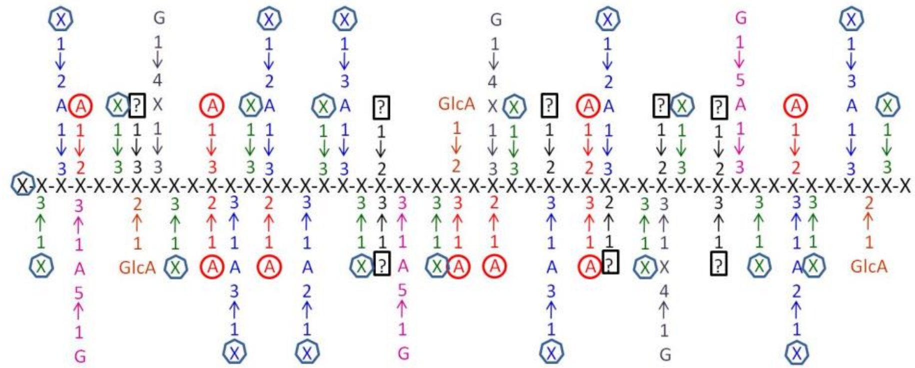
Arabinoxylans

Variability of structure among different cereal AXs influences fermentation rate

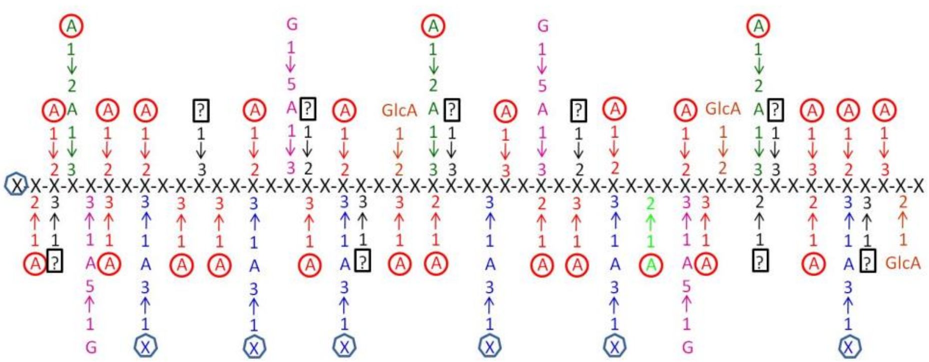
Sorghum



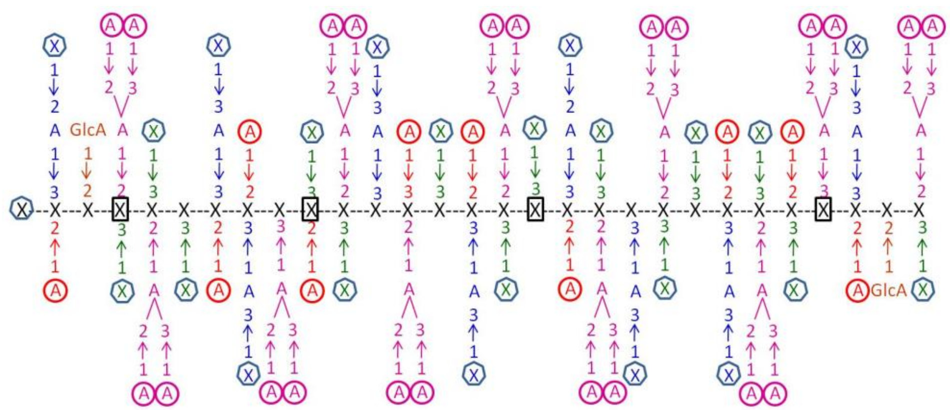
Corn Hydrolyzate



Rice Hydrolyzate



Wheat Fraction

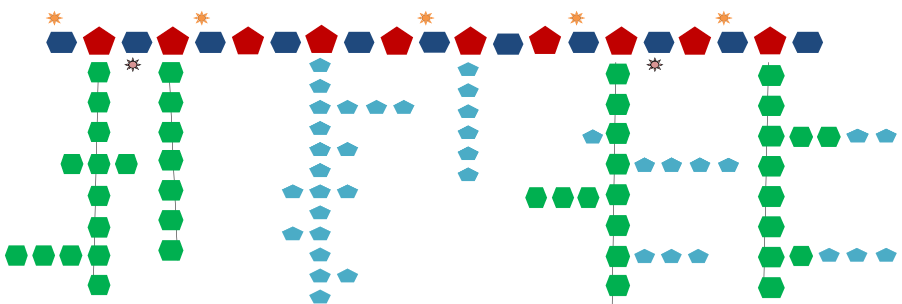


Pectins

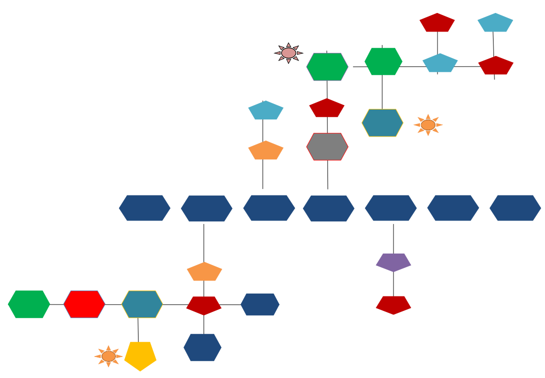
Homogalacturonan (HG)

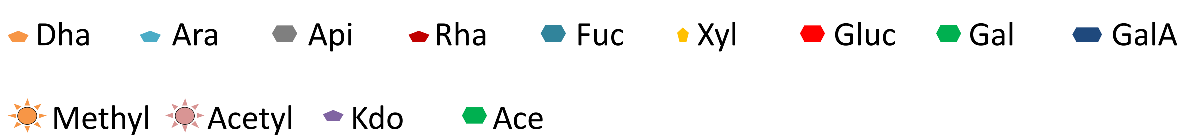
Xylogalacturonan (XG)

Rhamnogalacturonan I (RG I)



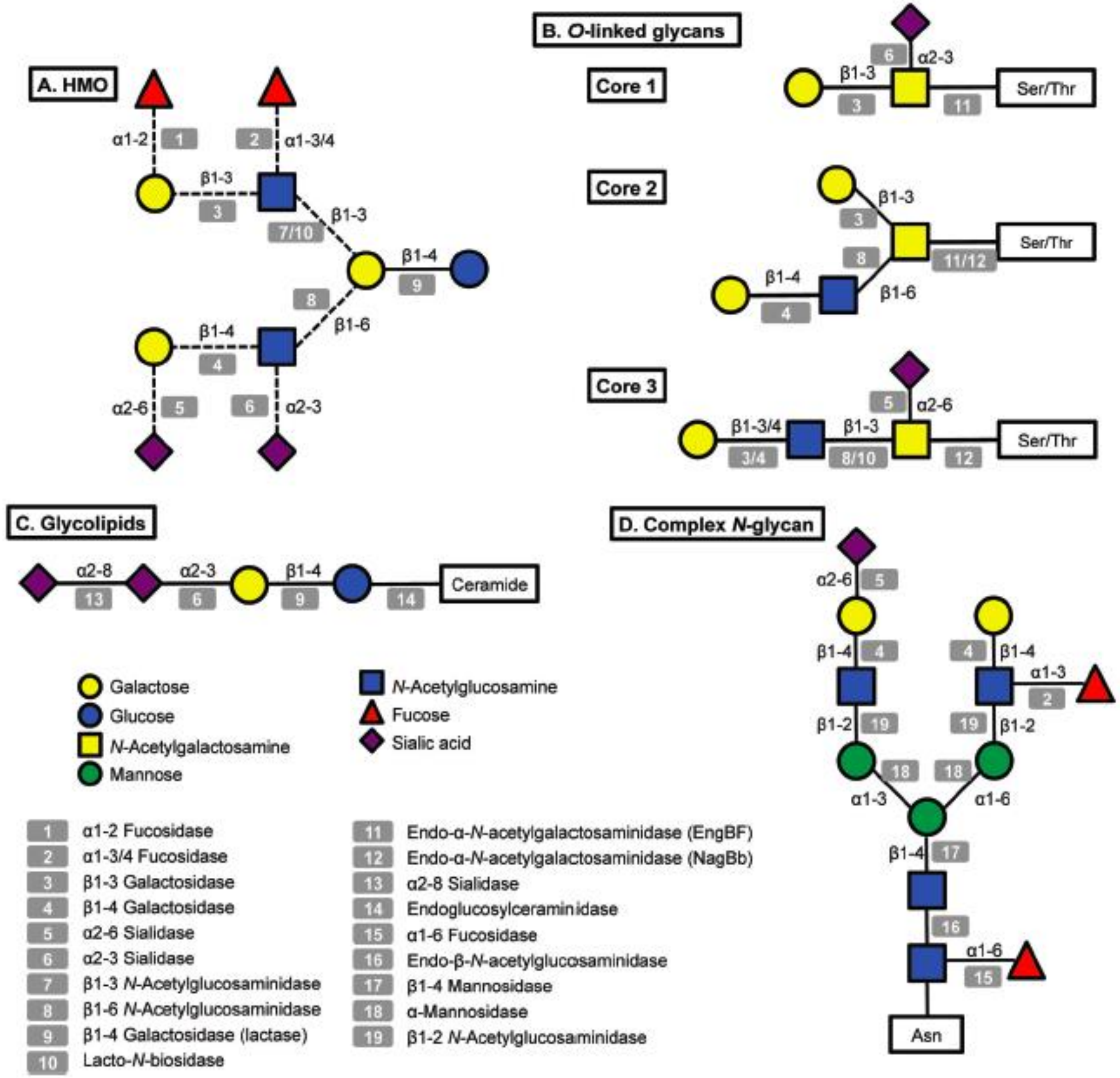
Rhamnogalacturonan II (RG II)





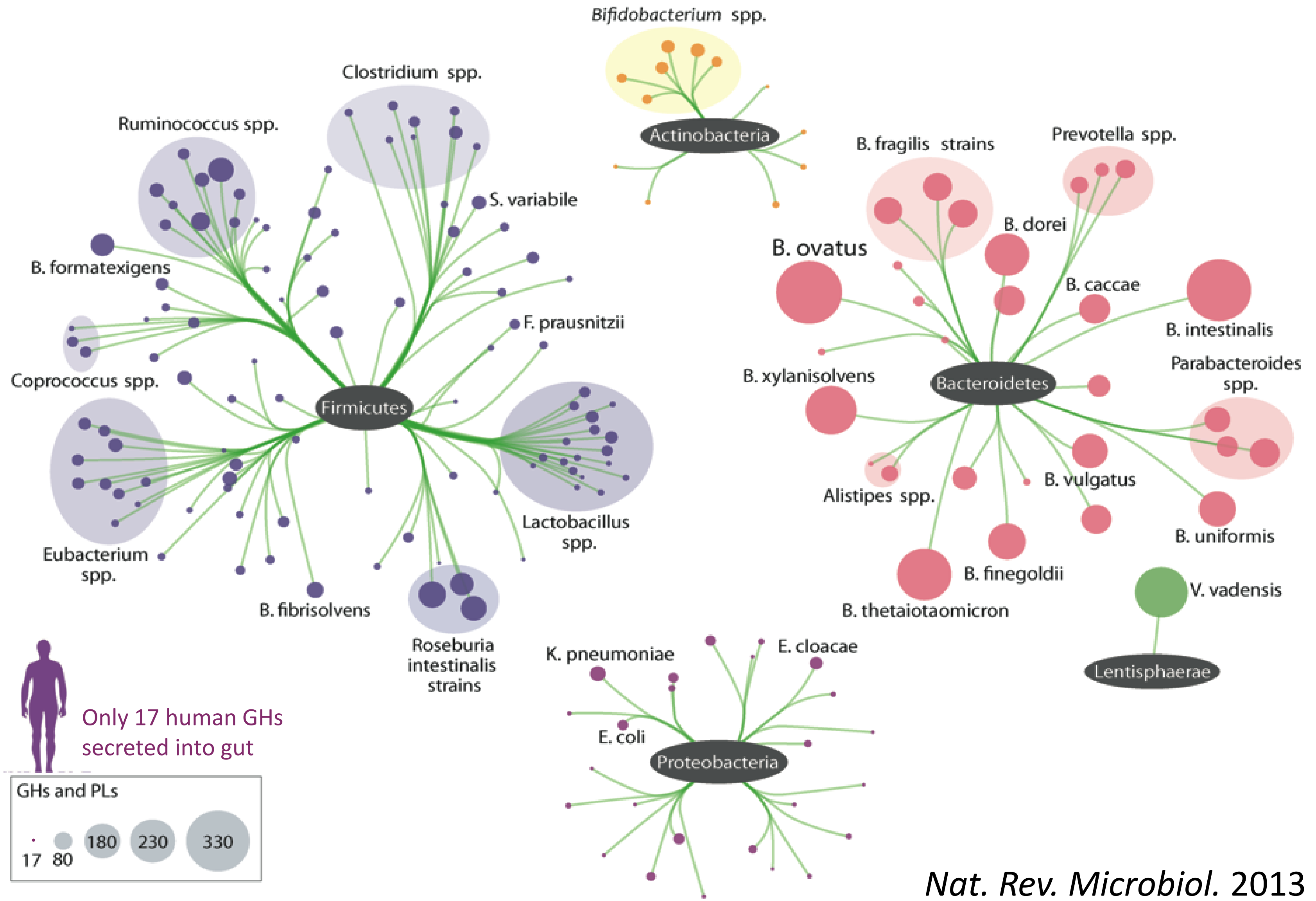
Human Milk Glycans

150 – 200 different HMO



Garrido et al Microbiology 2013

Human gut bacteria encode most of our polysaccharide digestive capacity

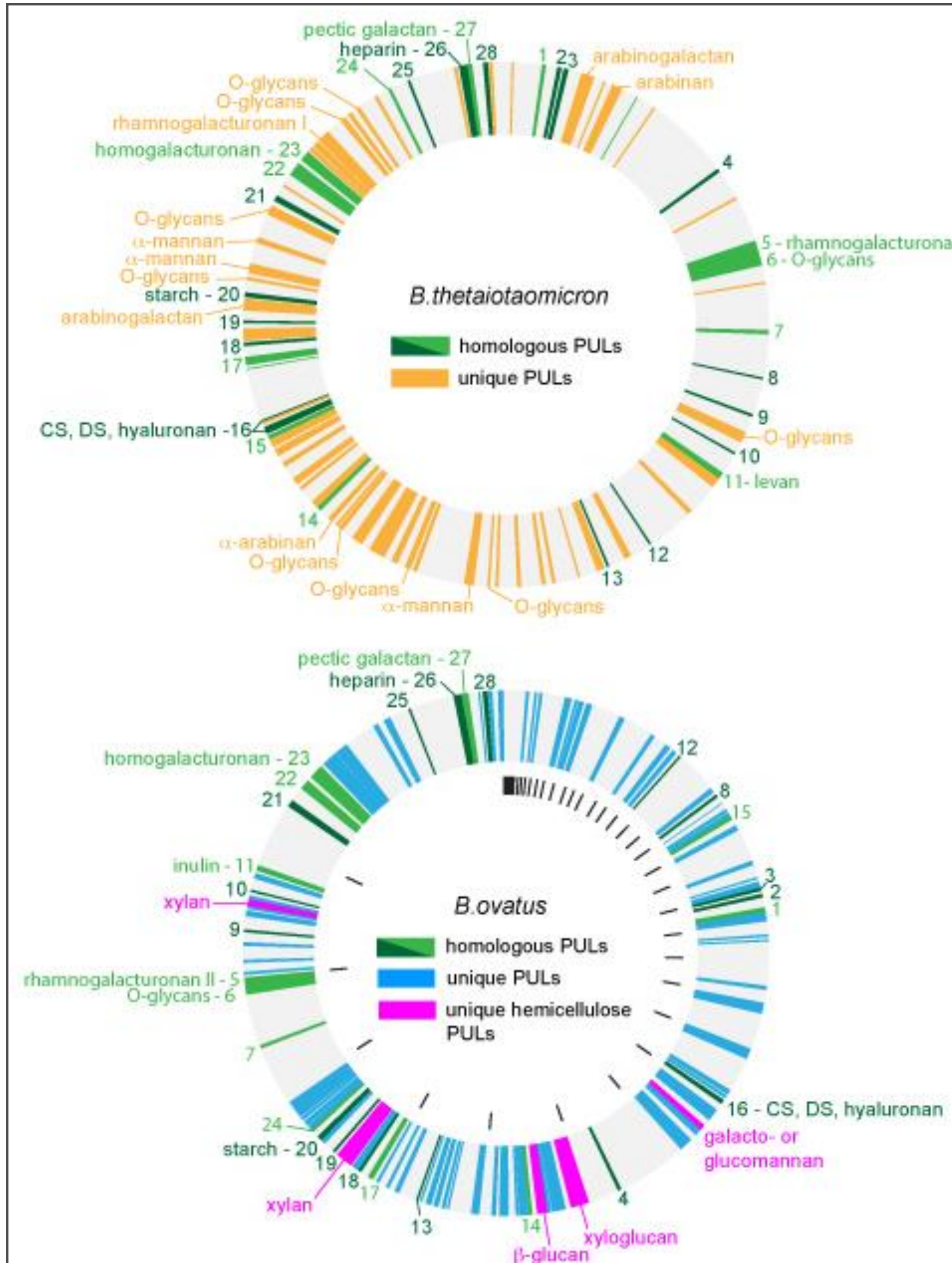


Nat. Rev. Microbiol. 2013

Matching genes to functions in gut symbionts reveals extensive, but only partially overlapping abilities

- *B. theta* and *B. ovatus* together degrade nearly all common dietary and host glycans
- 170 unique polysaccharide utilization loci (PULs)
- Each locus encodes functions for targeting a different polysaccharide
- Nearly 2,000 genes for carbohydrate processing

  (~650 enzymes)



PLoS Biology 2011

Take-home message #1

Chemistry Matters

- Cannot perform structure-function studies, metabolism studies, and mechanistic studies in the absence of analytical infrastructure
- Need to identify, characterize, quantify complex carbohydrates
- Prebiotic researchers needs investments (i.e., NIH, NSF) in glycomics and glycobiology

3. How are these effects manifested

- immune modulation

  SCFA

  antimicrobial peptides

  changes in the gut microbiota

- physiological effects

  metabolic syndrome
  gut-brain axis
  gut peptides

- anti-adherence

More take-home messages

2. Complex prebiotics may cross-feed and have unexpected outcomes
3. Rational synergistic synbiotics may provide a mechanism for successful introduction of probiotics
4. A multi-omics approach is necessary to understand the function of prebiotics in the gastrointestinal ecosystem and microbiota-host interactions