Development and Applications of the Community-based Ontology of Host-Microbiome Interactions (OHMI)

Yongqun "Oliver" He

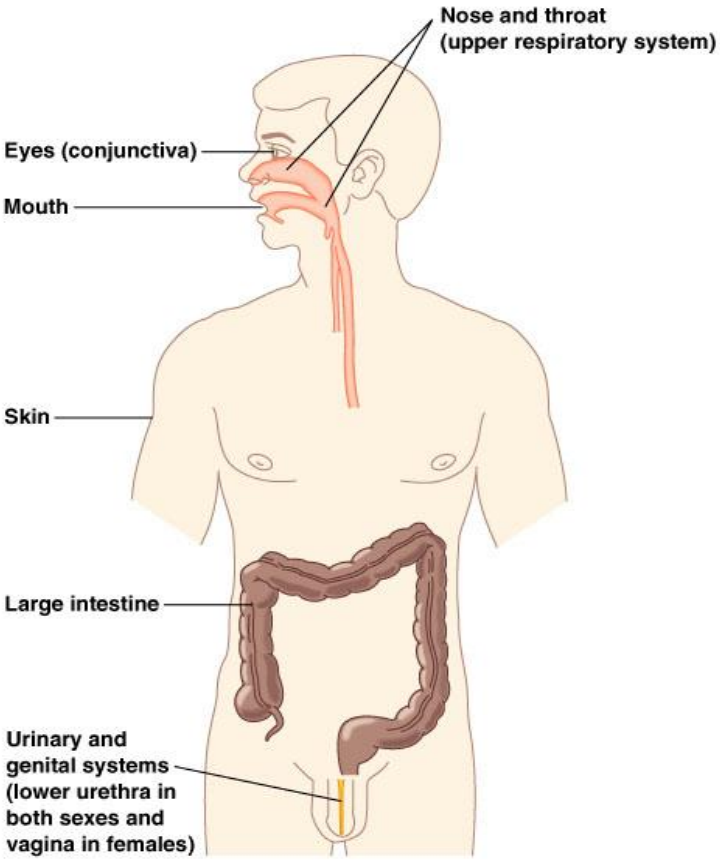
Unit for Laboratory Animal Medicine
Department of Microbiology and Immunology
Center for Computational Medicine and Bioinformatics
and Comprehensive Cancer Center
University of Michigan Medical School
Ann Arbor, MI 48109

UNIVERSITY OF
MICHIGAN

Normal Microbiota and the Host

- Locations of normal microbiota/microbiome on and in the human/host body

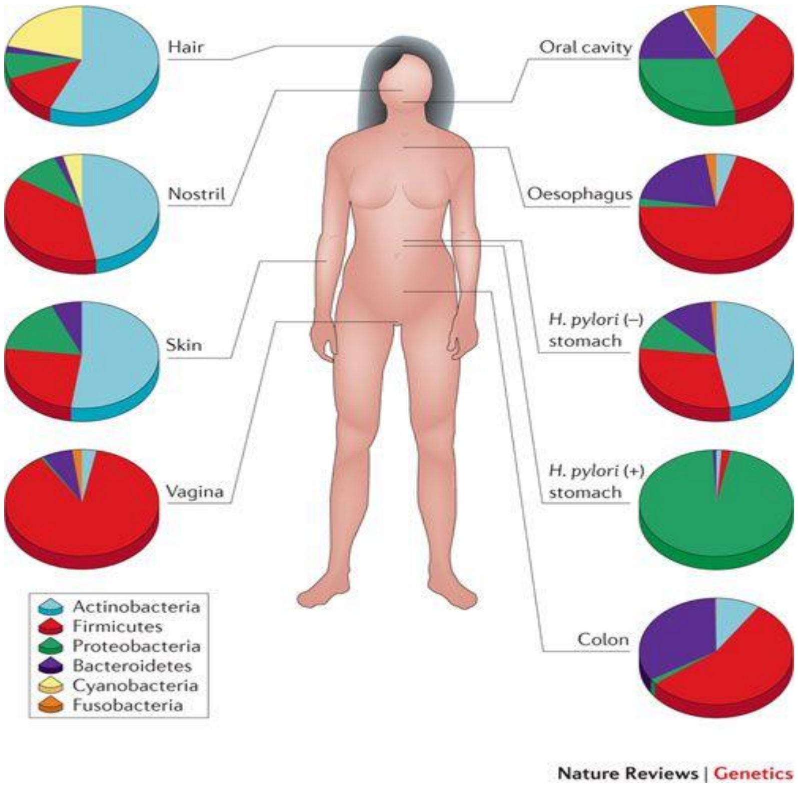
- Human body is built by **10 trillion** cells



- **100 trillion** non-pathogenic bacteria/microorganisms that reside in or on a human body

- Human body/commensal microbiota exist as a **community**

Host-microbiome interactions in different locations

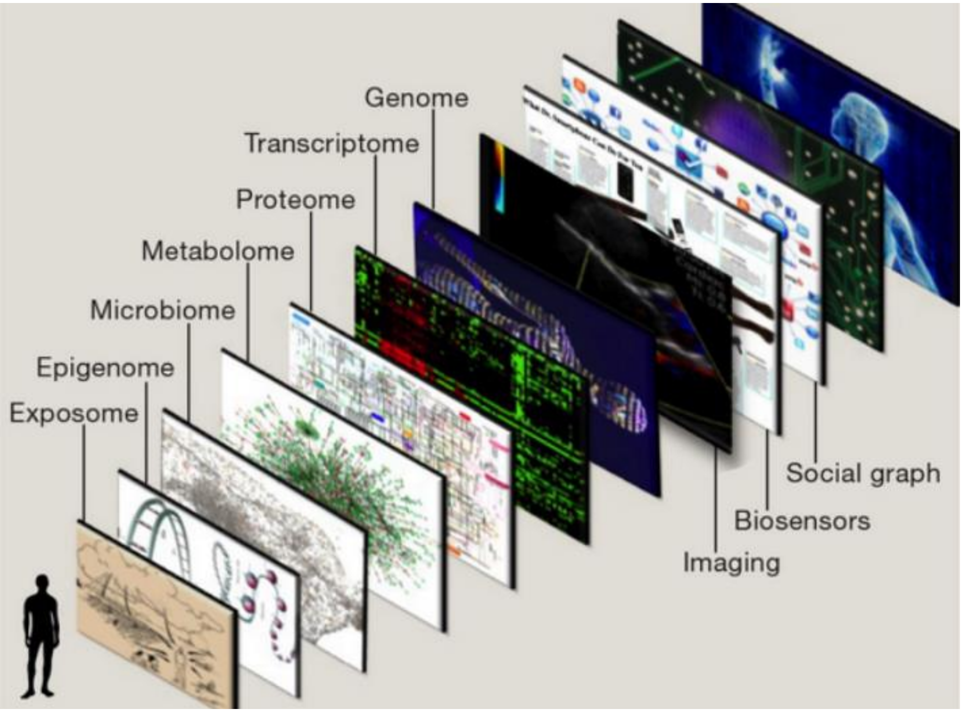


Nature Reviews | Genetics

- Microbial community vary at different body sites (*ecosystems*)
- Bacteria of a specific body site from different persons have more common characteristic (*common ecosystem*).
- The microbiome of a healthy and diseased person looks very different (*rearranged ecosystem*)

Issues in current HMI studies

- **Big data**
    - high volume, velocity, & variety
- **FAIR** data principles
    - **F**indable,
    - **A**ccessible,
    - **I**nteroperable,
    - **R**e-usable
- Hard to integrate various data, metadata, and knowledge



http://www.cell.com/cell/fulltext/S0092-8674(14)00204-9

OHMI introduction

- Aim: To ontologically represent various entities and relations related to **microbiomes**, microbiome **host** organisms (e.g., human and mouse), and the **interactions** between hosts and microbiomes at different **conditions**.
- Developed based on OBO principles.

GitHub: https://github.com/OHMI-ontology

Ontobee : http://www.ontobee.org/ontology/ohmi

BioPortal : http://bioportal.bioontology.org/ontologies/OHMI

Multi-Institutional Collaboration

University of Michigan

Yongqun "Oliver" He, DVM, PhD

Haihe Wang, MD, PhD (visiting scholar from Harbin Medical University, China)

Yu Hong, MD, PhD (visiting scholar from Guizhou Univ. Medical School, China)

Duke University

Anna Maria Masci, PhD

University of Pennsylvania

Jie Zheng, PhD

Daniel P Beiting, PhD

Medical University of South Carolina

Alexander V. Alekseyenko, PhD

Jihad S. Obeid, MD

OHMI Use Cases

- **Rheumatic diseases**: Literature mining, and 16S rRNA sequencing and analysis; more later in this talk. (**YH, HW, U Mich**)
- **RNAseq data**: Overarching use case for analyzing RNAseq for host gene expression and microbiome relation to human health, e.g. COPD and smoking and impact of microbiome. (**YH, HW, AA, JO, JZ, AM**)
- **Radiation induced oral mucositis (OM) development and treatment**: A clinical trial in treatment of OM and the role of microbiota in etiology. The microbiome in the oral cavity is shaped by the anatomical location and is highly dynamic in response to treatment. (**AA, JO, MUSC**)
- **Microbiome and immunity in colorectal cancer disparities**: Study the relationship between specific microbiota and host immune gene expression to determine the relationships between the two that shape the disparities in colorectal cancer between African American and Caucasian patients. (**AA, JO, MUSC**)
- **MicrobiomeDB** (http://microbiomedb.org/mbio/): Ontology used for indexing, searches and metadata analysis. (**JZ, DP, U Penn**)
- **GVHD-microbiome interactions**: Annotation of Graft-Versus-Host Disease (GVHD) data and role of microbiome population in the disease. (**AM, Duke**).

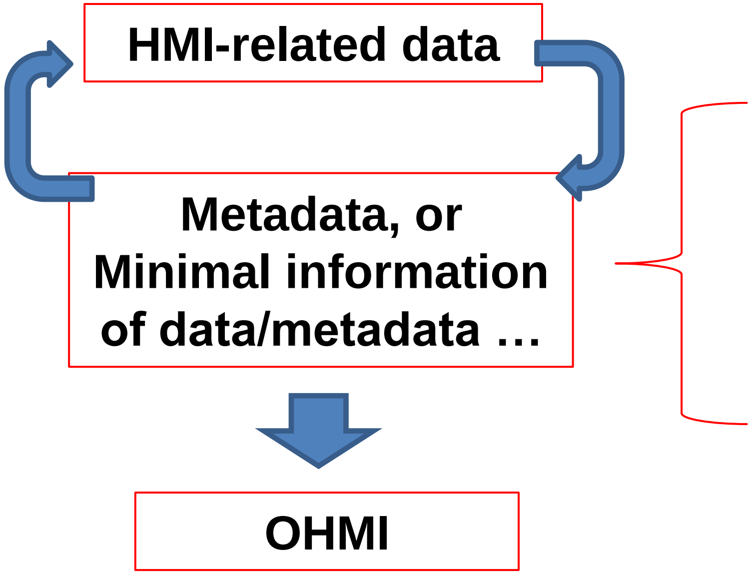
Related Ontologies

- ***MicrO***: Ontology of Prokaryotic Phenotypic and Metabolic Characters, published last year. (https://github.com/carrineblank/MicrO/)
- ***OMP***: Ontology for Microbial Phenotypes, Texas A&M University. (https://microbialphenotypes.org)
- ***MEOWL***: Microbial Environments described using OWL, by Ramona L. Walls. (https://github.com/hurwitzlab/meowl)
- ***ENVO:*** Environment Ontology
- ***OBI***: Ontology for Biomedical Investigations
- **DOID**: Disease Ontology

These ontologies do not focus on host-microbiome interactions. Meanwhile, **OHMI reuses these ontologies**.

OHMI for standardization metadata used in host-microbiome interaction studies

HMI data science research:



HMI-related data

Metadata, or Minimal information of data/metadata …

OHMI

Genome sequencing (MIxS, …)

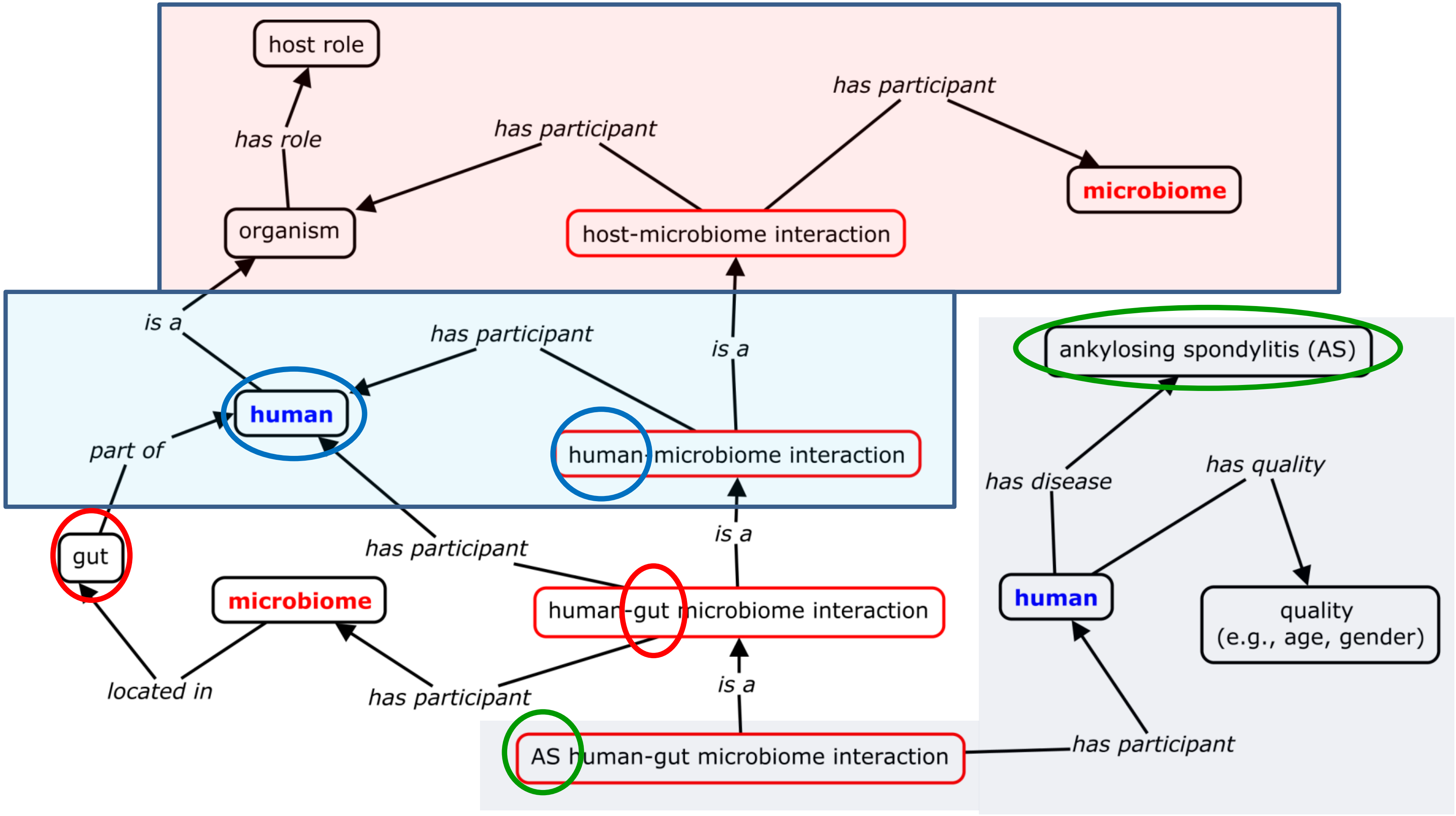
Flow Cytometry

Clinical …

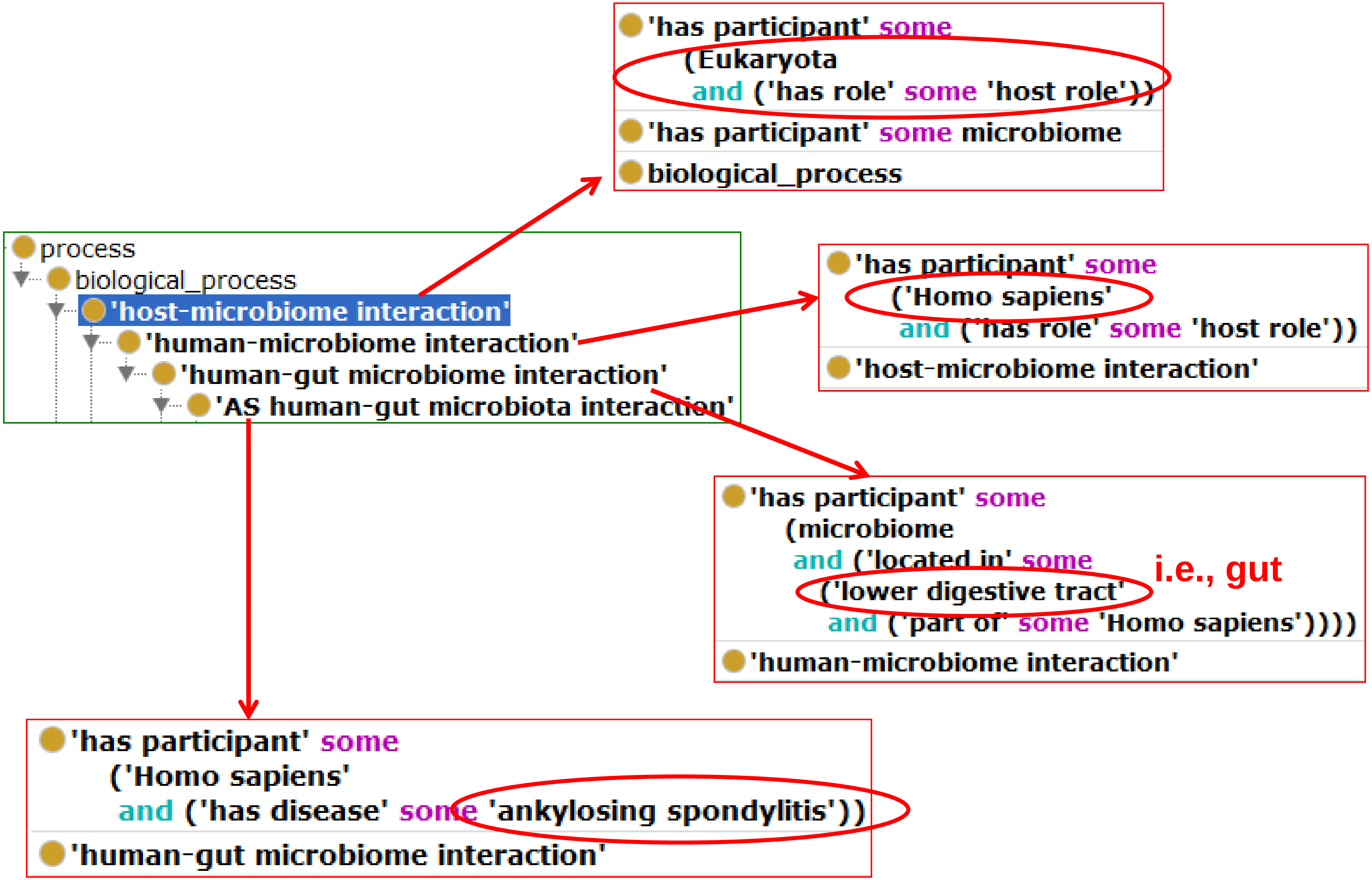
For standardizing and integrating HMI data

OHMI host-microbiome interaction (HMI) terms

- HMI has participants which may differ:
  - host organism (has disease, age, gender, …)
  - microbiome (in a location, has bacterium or virus, …)



OHMI HMI design pattern



- process
  - biological_process
    - 'host-microbiome interaction'
      - 'human-microbiome interaction'
        - 'human-gut microbiome interaction'
          - 'AS human-gut microbiota interaction'

● 'has participant' some
(Eukaryota
and ('has role' some 'host role'))
● 'has participant' some microbiome
● biological_process

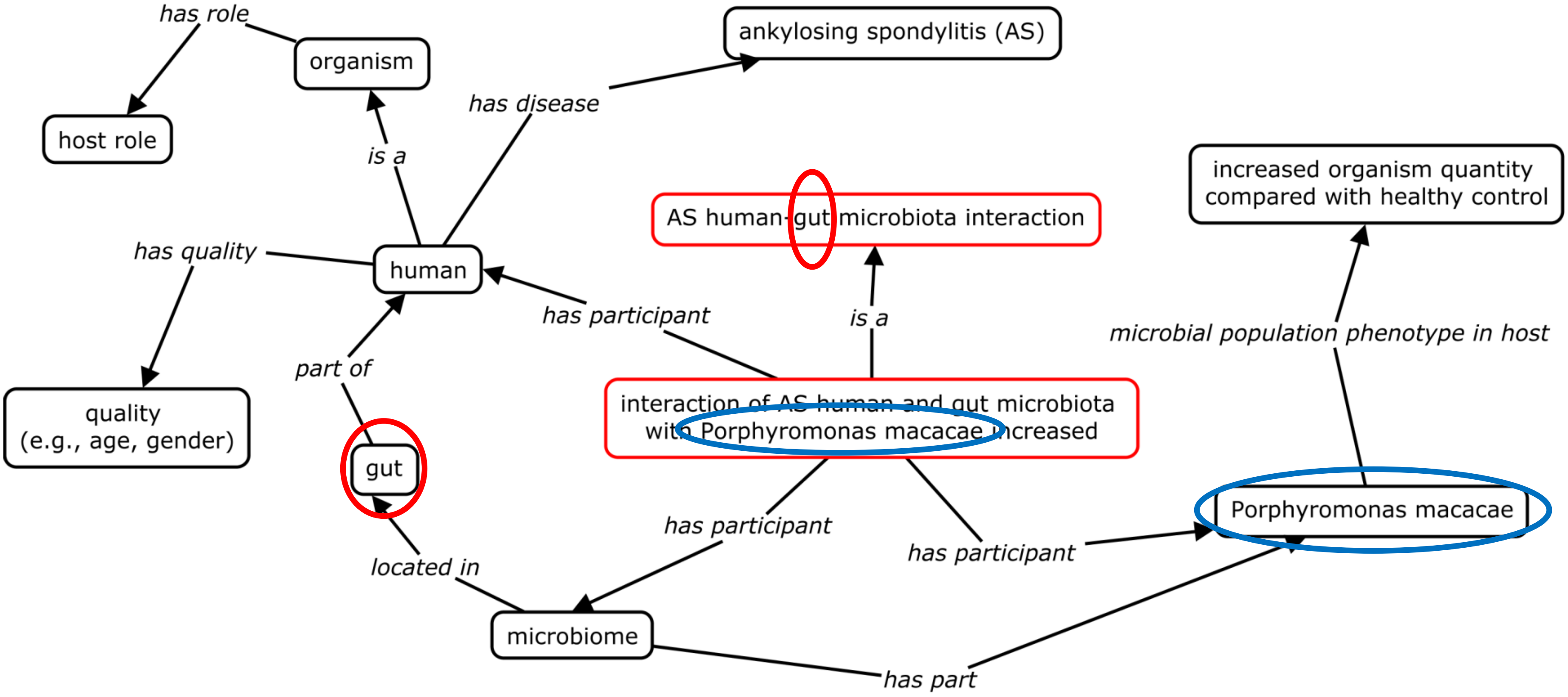
● 'has participant' some
('Homo sapiens'
and ('has role' some 'host role'))
● 'host-microbiome interaction'

● 'has participant' some
(microbiome
and ('located in' some
('lower digestive tract'
and ('part of' some 'Homo sapiens'))))
● 'human-microbiome interaction'

i.e., gut

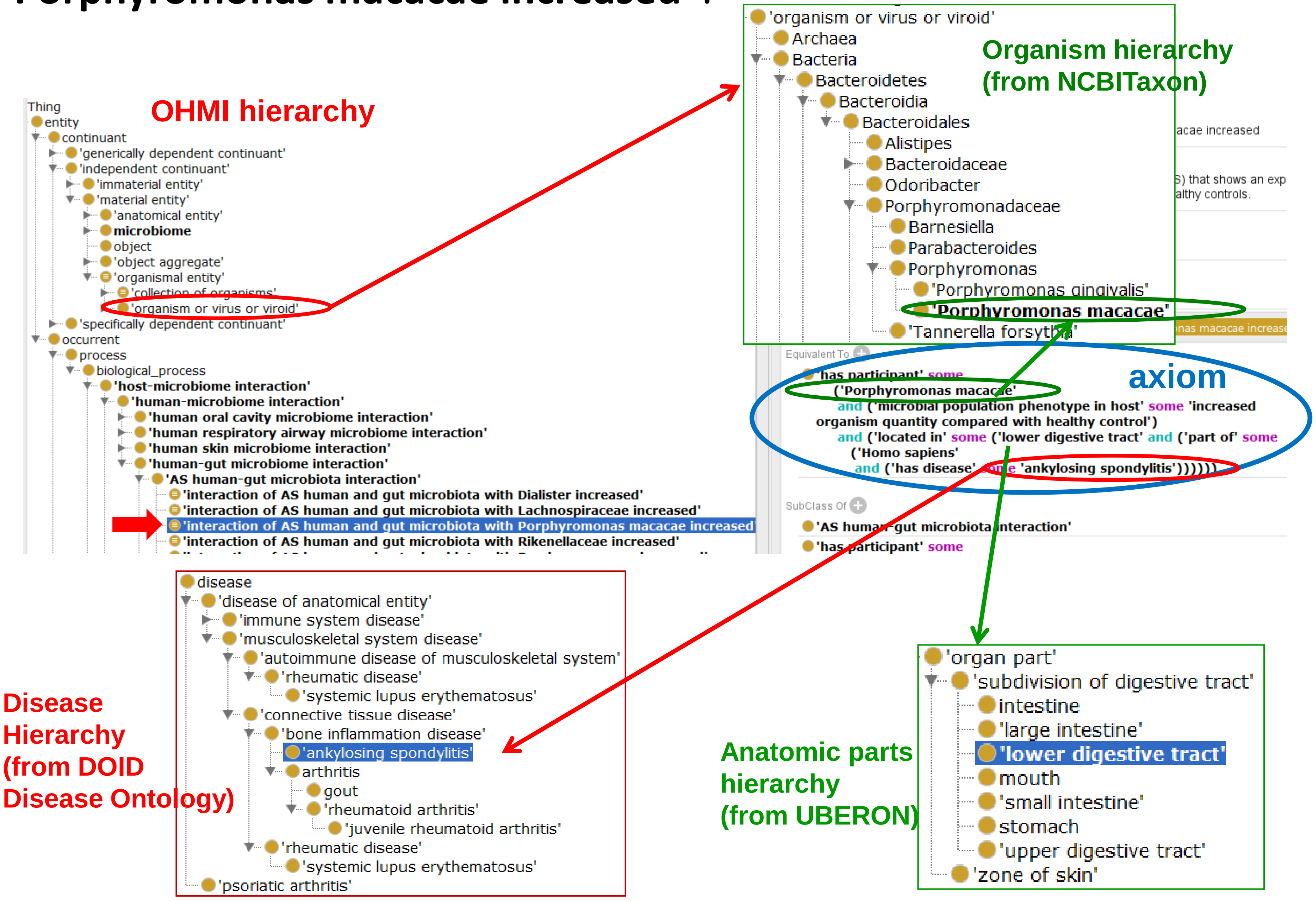
● 'has participant' some
('Homo sapiens'
and ('has disease' some 'ankylosing spondylitis'))
● 'human-gut microbiome interaction'

OHMI model "interaction of AS human and gut microbiota with *Porphyromonas macacae* increased"



AS: Ankylosing Spondylitis

Example: “**interaction of AS human and gut microbiota with Porphyromonas macacae increased**”:



OHMI hierarchy

- Thing
  - entity
    - continuant
      - 'generically dependent continuant'
      - 'independent continuant'
        - 'immaterial entity'
        - 'material entity'
          - 'anatomical entity'
          - **microbiome**
          - object
          - 'object aggregate'
          - 'organismal entity'
            - 'collection of organisms'
            - 'organism or virus or viroid'
      - 'specifically dependent continuant'
    - occurrent
      - process
        - biological_process
          - **'host-microbiome interaction'**
            - **'human-microbiome interaction'**
              - **'human oral cavity microbiome interaction'**
              - **'human respiratory airway microbiome interaction'**
              - **'human skin microbiome interaction'**
              - **'human-gut microbiome interaction'**
                - **'AS human-gut microbiota interaction'**
                  - **'interaction of AS human and gut microbiota with Dialister increased'**
                  - **'interaction of AS human and gut microbiota with Lachnospiraceae increased'**
                  - **'interaction of AS human and gut microbiota with Porphyromonas macacae increased'**
                  - **'interaction of AS human and gut microbiota with Rikenellaceae increased'**

Organism hierarchy (from NCBITaxon)

- 'organism or virus or viroid'
  - Archaea
  - Bacteria
    - Bacteroidetes
      - Bacteroidia
        - Bacteroidales
          - Alistipes
          - Bacteroidaceae
          - Odoribacter
          - Porphyromonadaceae
            - Barnesiella
            - Parabacteroides
            - Porphyromonas
              - 'Porphyromonas gingivalis'
              - **'Porphyromonas macacae'**
            - 'Tannerella forsythia'

acae increased

S) that shows an exp
althy controls.

nas macacae increase

axiom

Equivalent To

'has participant' some
('Porphyromonas macacae'
and ('microbial population phenotype in host' some 'increased organism quantity compared with healthy control')
and ('located in' some ('lower digestive tract' and ('part of' some
('Homo sapiens'
and ('has disease' some 'ankylosing spondylitis'))))))

SubClass Of

'AS human-gut microbiota interaction'

'has participant' some

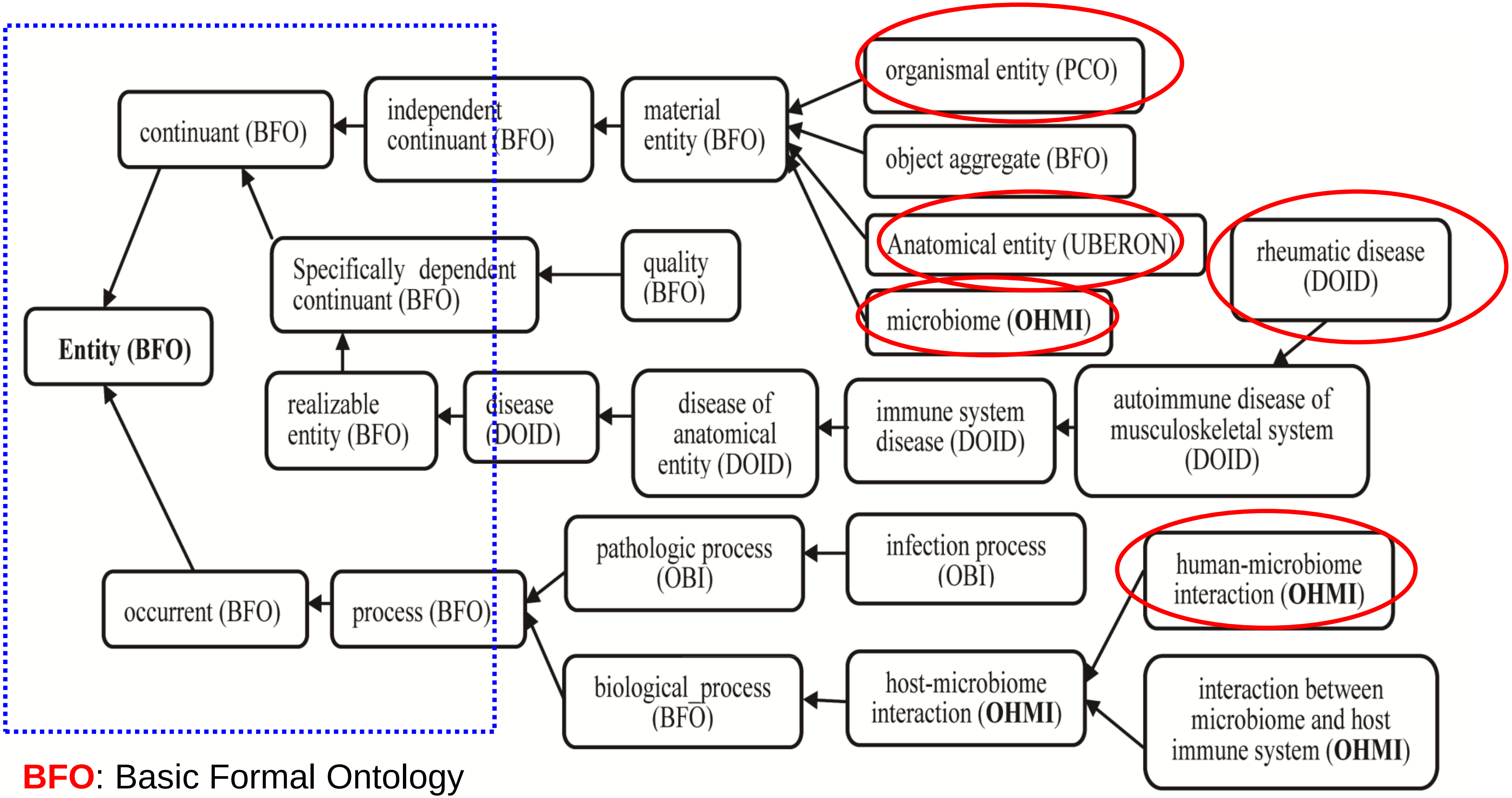
Disease Hierarchy (from DOID Disease Ontology)

- disease
  - 'disease of anatomical entity'
    - 'immune system disease'
    - 'musculoskeletal system disease'
      - 'autoimmune disease of musculoskeletal system'
        - 'rheumatic disease'
          - 'systemic lupus erythematosus'
      - 'connective tissue disease'
        - 'bone inflammation disease'
          - 'ankylosing spondylitis'
          - arthritis
            - gout
            - 'rheumatoid arthritis'
              - 'juvenile rheumatoid arthritis'
        - 'rheumatic disease'
          - 'systemic lupus erythematosus'
  - 'psoriatic arthritis'

Anatomic parts hierarchy (from UBERON)

- 'organ part'
  - 'subdivision of digestive tract'
    - intestine
    - 'large intestine'
    - 'lower digestive tract'
    - mouth
    - 'small intestine'
    - stomach
    - 'upper digestive tract'
  - 'zone of skin'

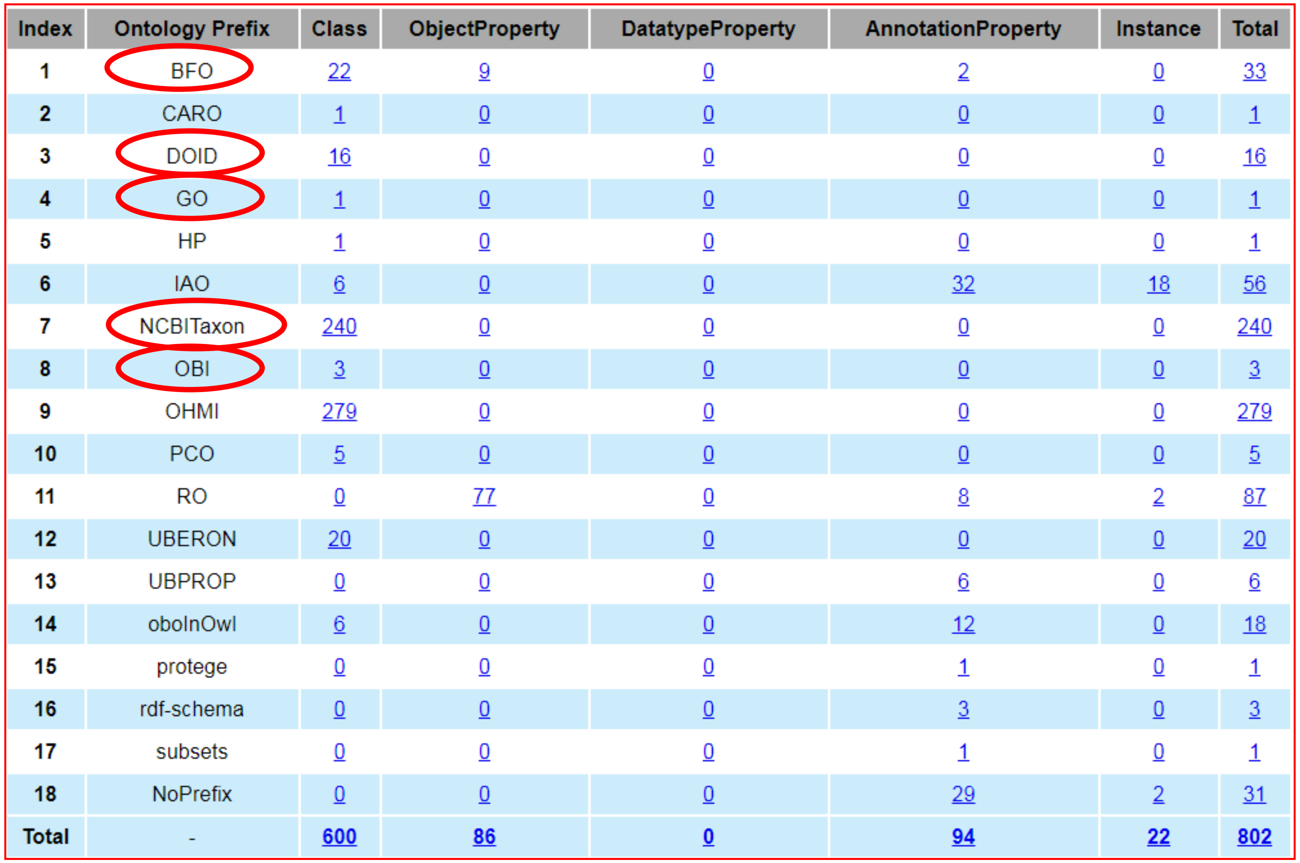
OHMI top level hierarchy design



BFO: Basic Formal Ontology
(an upper level ontology)

OHMI ontology statistics

- Total: **802** terms
- Reuse >10 ontologies:
  - BFO (Basic Formal Ontology)
  - GO (Gene Ontology)
  - DOID (Disease Ontology)
  - NCBITaxon (NCBI Taxonomy O.)
  - OBI (O. for Biomedical Investigations)
- 279 new terms



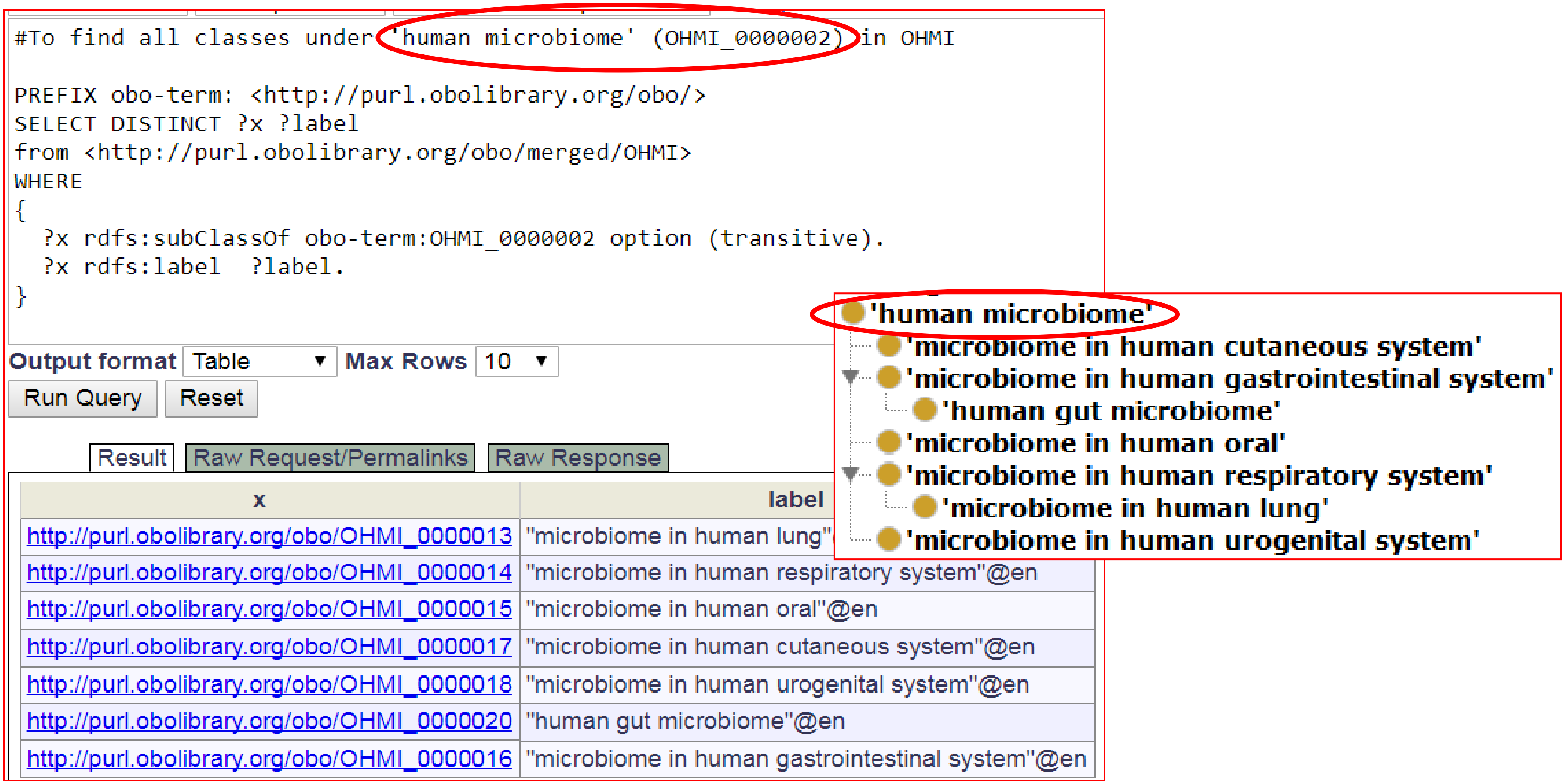
Index	Ontology Prefix	Class	ObjectProperty	DatatypeProperty	AnnotationProperty	Instance	Total
1	BFO	22	9	0	2	0	33
2	CARO	1	0	0	0	0	1
3	DOID	16	0	0	0	0	16
4	GO	1	0	0	0	0	1
5	HP	1	0	0	0	0	1
6	IAO	6	0	0	32	18	56
7	NCBITaxon	240	0	0	0	0	240
8	OBI	3	0	0	0	0	3
9	OHMI	279	0	0	0	0	279
10	PCO	5	0	0	0	0	5
11	RO	0	77	0	8	2	87
12	UBERON	20	0	0	0	0	20
13	UBPROP	0	0	0	6	0	6
14	oboInOwl	6	0	0	12	0	18
15	protege	0	0	0	1	0	1
16	rdf-schema	0	0	0	3	0	3
17	subsets	0	0	0	1	0	1
18	NoPrefix	0	0	0	29	2	31
Total	-	**600**	**86**	**0**	**94**	**22**	**802**

http://www.ontobee.org/ontostat/OHMI

OHMI SPARQL query

SPARQL: Query language for ontology after stored in RDF triple store
RDF: Resource Description Framework *(triple: subject–predicate–object)*

Example: Find all classes under ‘human microbiome’:



```
#To find all classes under 'human microbiome' (OHMI_0000002) in OHMI

PREFIX obo-term: <http://purl.obolibrary.org/obo/>
SELECT DISTINCT ?x ?label
from <http://purl.obolibrary.org/obo/merged/OHMI>
WHERE
{
  ?x rdfs:subClassOf obo-term:OHMI_0000002 option (transitive).
  ?x rdfs:label  ?label.
}
```

Output format: Table
Max Rows: 10

x	label
http://purl.obolibrary.org/obo/OHMI_0000013	"microbiome in human lung"@en
http://purl.obolibrary.org/obo/OHMI_0000014	"microbiome in human respiratory system"@en
http://purl.obolibrary.org/obo/OHMI_0000015	"microbiome in human oral"@en
http://purl.obolibrary.org/obo/OHMI_0000017	"microbiome in human cutaneous system"@en
http://purl.obolibrary.org/obo/OHMI_0000018	"microbiome in human urogenital system"@en
http://purl.obolibrary.org/obo/OHMI_0000020	"human gut microbiome"@en
http://purl.obolibrary.org/obo/OHMI_0000016	"microbiome in human gastrointestinal system"@en

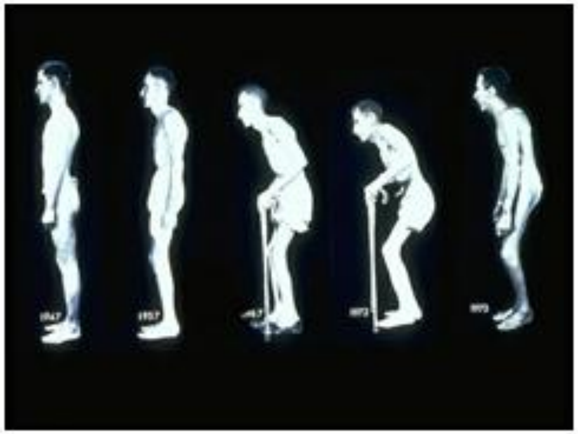
- **'human microbiome'**
  - **'microbiome in human cutaneous system'**
  - **'microbiome in human gastrointestinal system'**
    - **'human gut microbiome'**
  - **'microbiome in human oral'**
  - **'microbiome in human respiratory system'**
    - **'microbiome in human lung'**
  - **'microbiome in human urogenital system'**

Rheumatic diseases

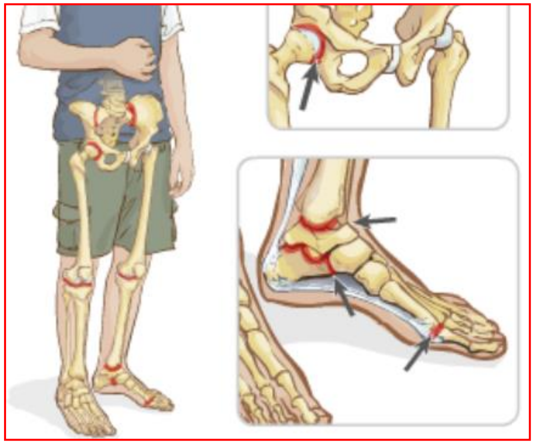
- Rheumatism represents any disease condition marked with inflammation and pain in the joints, muscles, or connective tissues.
- *Six rheumatic diseases used:*
  - Rheumatoid Arthritis (**RA**)
  - Ankylosing Spondylitis (**AS**)
  - Systemic Lupus Erythematosus (**SLE**)
  - Psoriatic arthritis (**PsA**)
  - Gout
  - Juvenile Enthesitis-related Arthritis (**ERA**)

Various Rheumatic Diseases

RA



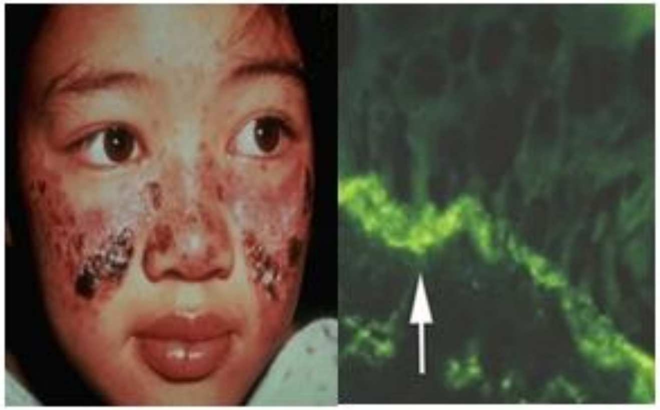
AS



ERA

Gout

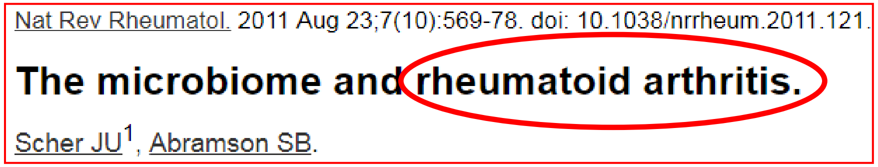
PsA



SLE

Rheumatic diseases and Microbiomes

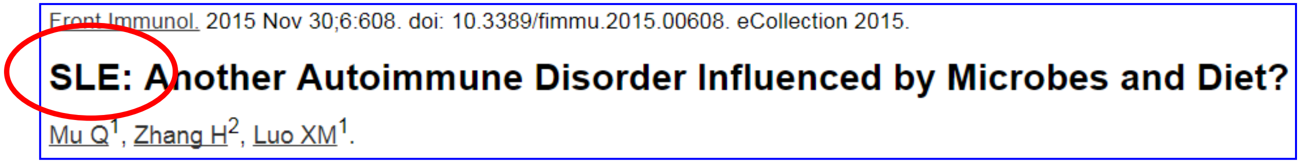
- Rheumatic diseases found to be influenced by microbiomes
- What really happen? Can we use OHMI to study?



Nat Rev Rheumatol. 2011 Aug 23;7(10):569-78. doi: 10.1038/nrrheum.2011.121.

The microbiome and rheumatoid arthritis.

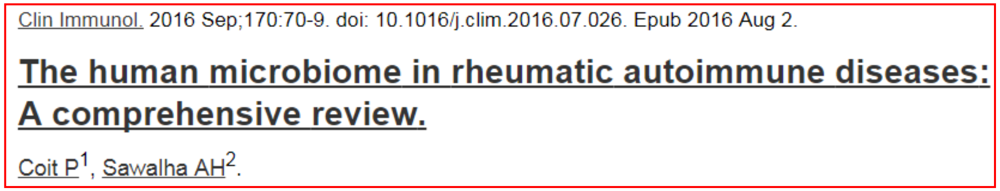
Scher JU[1], Abramson SB.



Front Immunol. 2015 Nov 30;6:608. doi: 10.3389/fimmu.2015.00608. eCollection 2015.

SLE: Another Autoimmune Disorder Influenced by Microbes and Diet?

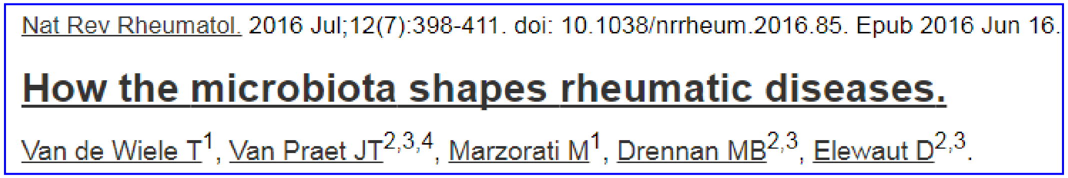
Mu Q[1], Zhang H[2], Luo XM[1].



Clin Immunol. 2016 Sep;170:70-9. doi: 10.1016/j.clim.2016.07.026. Epub 2016 Aug 2.

The human microbiome in rheumatic autoimmune diseases: A comprehensive review.

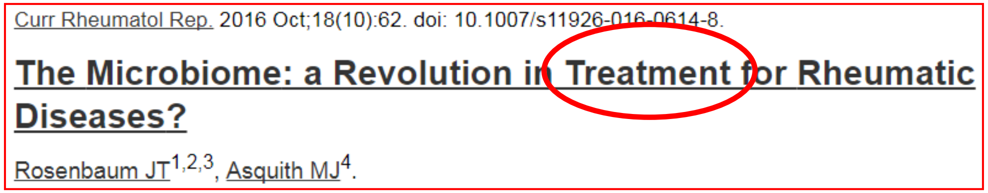
Coit P[1], Sawalha AH[2].



Nat Rev Rheumatol. 2016 Jul;12(7):398-411. doi: 10.1038/nrrheum.2016.85. Epub 2016 Jun 16.

How the microbiota shapes rheumatic diseases.

Van de Wiele T[1], Van Praet JT[2,3,4], Marzorati M[1], Drennan MB[2,3], Elewaut D[2,3].



Curr Rheumatol Rep. 2016 Oct;18(10):62. doi: 10.1007/s11926-016-0614-8.

The Microbiome: a Revolution in Treatment for Rheumatic Diseases?

Rosenbaum JT[1,2,3], Asquith MJ[4].

HMI role in pathogenesis of rheumatic diseases

Genetic/environ. factors

dysbiosis

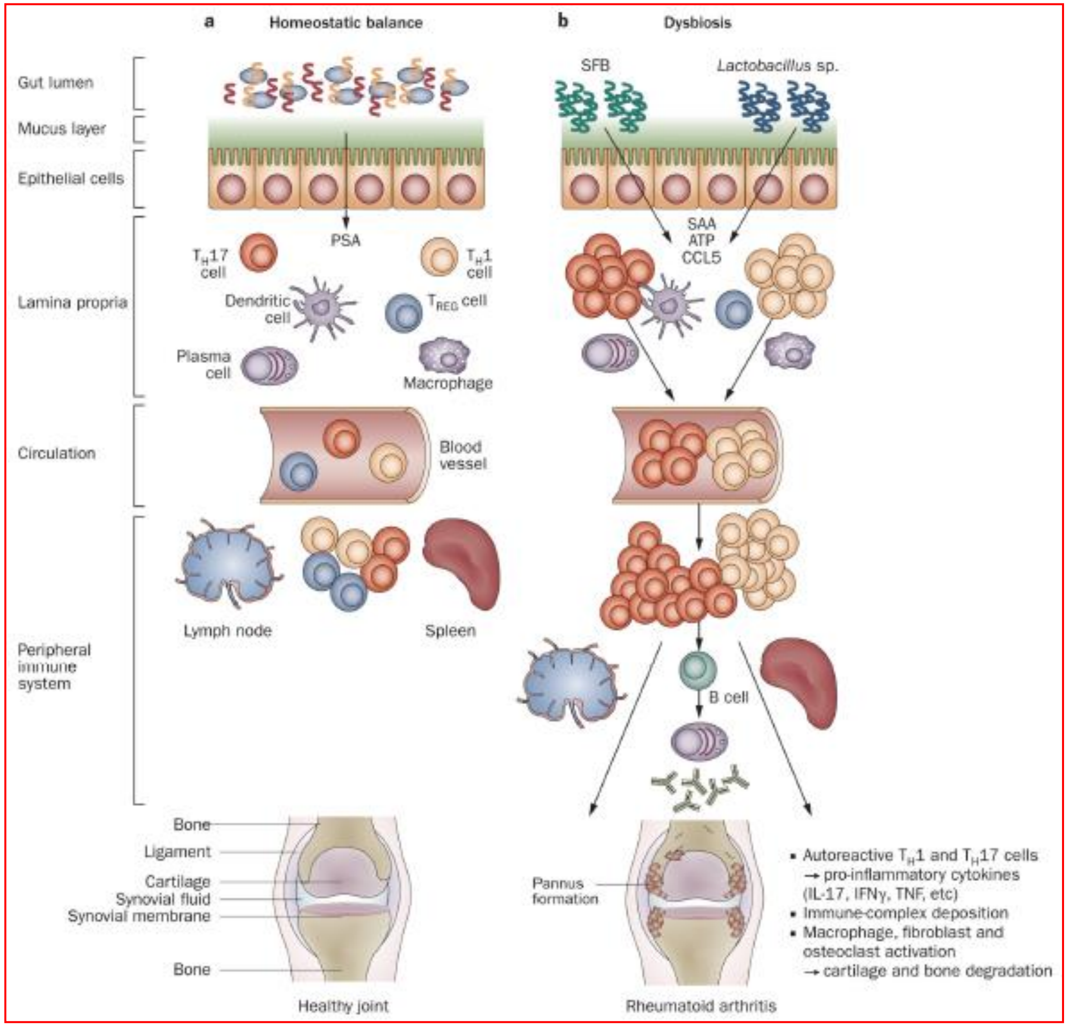
Harmful microbes predominate

Proinflammatory T cells (Th1, Th17) expand and migrate

B cells activated → autoantibodies and migrate

Inflammatory cascade in synovial tissues

RA formation

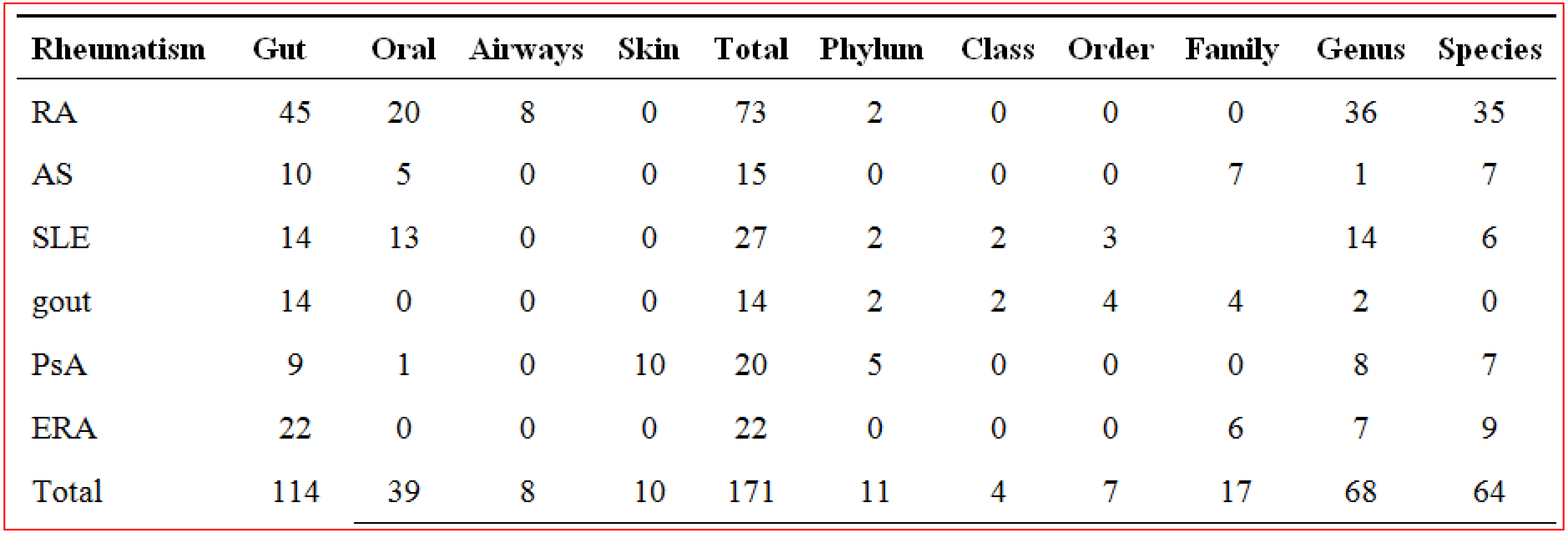


Scher JU and Abramson SB. The microbiome and rheumatoid arthritis. *Nat Rev Rheumatol*. 2011. 7(10): 569–578.

OHMI HMI study on rheumatic diseases

- Two studies to present here
- **OHMI-based meta-analysis**:
  1) HMI literature annotation
  2) OHMI representation of annotated results
  3) OHMI-based analysis
- **Ankylosing Spondylitis (AS) study:**
  1) 16S rRNA sequencing + clinical observation
  2) Common 16S rRNA sequence analysis
  3) Bayesian network analysis

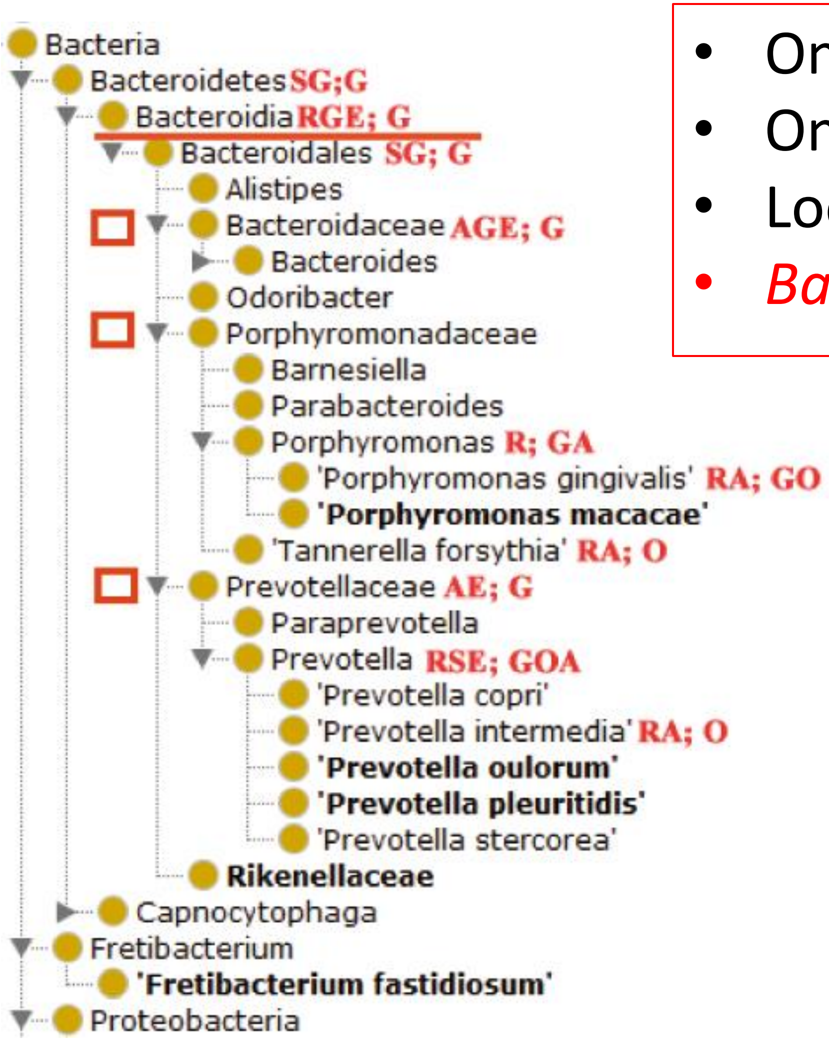
Literature: 171 microbes increased/decreased in microbiota of rheumatic disease patients



Rheumatism	Gut	Oral	Airways	Skin	Total	Phylum	Class	Order	Family	Genus	Species
RA	45	20	8	0	73	2	0	0	0	36	35
AS	10	5	0	0	15	0	0	0	7	1	7
SLE	14	13	0	0	27	2	2	3		14	6
gout	14	0	0	0	14	2	2	4	4	2	0
PsA	9	1	0	10	20	5	0	0	0	8	7
ERA	22	0	0	0	22	0	0	0	6	7	9
Total	114	39	8	10	171	11	4	7	17	68	64

- **Mostly bacteria**
- **2 fungi**: *Candida albicans* and *Diutina rugosa*

Many bacteria in different diseases



- Bacteria
  - Bacteroidetes SG;G
    - Bacteroidia RGE; G
      - Bacteroidales SG; G
        - Alistipes
        - Bacteroidaceae AGE; G
          - Bacteroides
        - Odoribacter
        - Porphyromonadaceae
          - Barnesiella
          - Parabacteroides
          - Porphyromonas R; GA
            - 'Porphyromonas gingivalis' RA; GO
            - **'Porphyromonas macacae'**
          - 'Tannerella forsythia' RA; O
        - Prevotellaceae AE; G
          - Paraprevotella
          - Prevotella RSE; GOA
            - 'Prevotella copri'
            - 'Prevotella intermedia' RA; O
            - **'Prevotella oulorum'**
            - **'Prevotella pleuritidis'**
            - 'Prevotella stercorea'
        - **Rikenellaceae**
    - Capnocytophaga
  - Fretibacterium
    - **'Fretibacterium fastidiosum'**
  - Proteobacteria

- One bacterium - many diseases
- One disease - many bacteria –
- Locations may differ
- *Bacteroidetes* is a major branch

Diseases:

A: AS; **E**: ELA; **G**: Gout; **P**: PsA; **R**: RA; **S**: SLE

Locations:

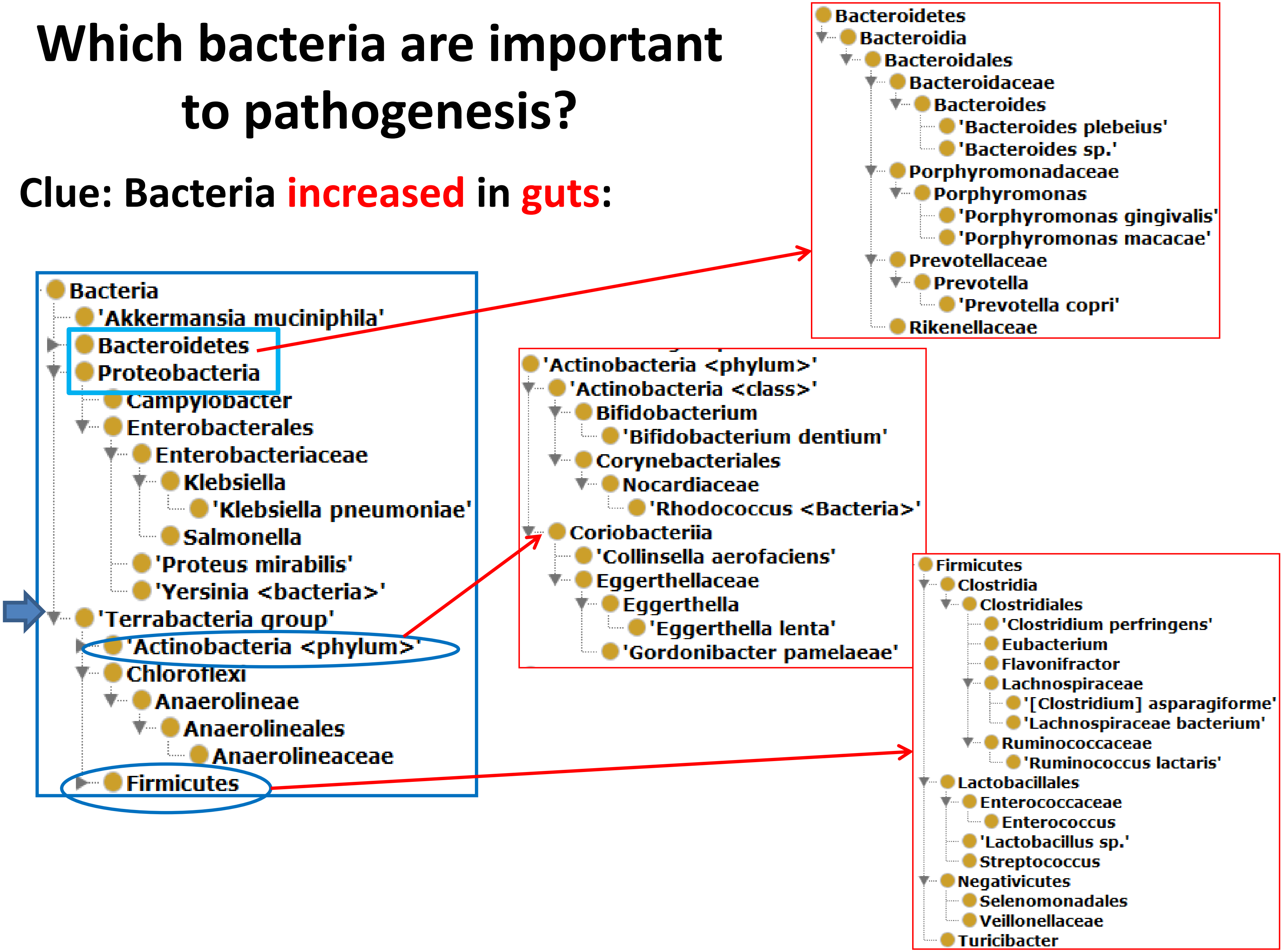
A: Air; **G**: Gut; **O**: Oral;

21 bacteria in >=2 rheumatic diseases

Number	Bacteria name	Rank	RA	AS	SLE	Gout	PsA	ERA	Gut	Oral	Airways	Skin
1	Klebsiella pneumoniae	species	RA	AS					gut	oral		
2	Haemophilus sp	species	RA						gut	oral		
3	Porphyromonas gingivalis	species	RA	AS					gut	oral		
4	Candida albicans	specices					PsA		gut	oral		
5	Tannerella forsythia	species	RA	AS						oral		
6	Prevotella intermedia	species	RA	AS						oral		
7	Collinsella aerofaciens	species	RA						gut	oral		
8	Clostridia	species	RA		SLE				gut			
9	Eleutherodactylus lentus	species	RA						gut	oral		
10	Prevotella	genus	RA		SLE			ERA	gut	oral	airways	
11	Bacteroides	genus	RA			gout		ERA	gut			
12	Porphyromonas	genus	RA						gut		airways	
13	Treponema	genus	RA		SLE					oral	airways	
14	Klebsiella	genus			SLE			ERA	gut			
15	Haemophilus	genus	RA						gut	oral		
16	Streptococcus	genus	RA				PsA		gut			skin
17	Actinomyces	genus	RA							oral	airways	
18	Rhodococcus	genus			SLE	gout			gut			
19	Dialister	genus	RA	AS	SLE				gut			
20	Pseudobutyrivibrio	genus			SLE		PsA		gut			
21	Lachnospiraceae	family		AS				ERA	gut			

Which bacteria are important to pathogenesis?

Clue: Bacteria increased in guts:



- Bacteria
  - 'Akkermansia muciniphila'
  - Bacteroidetes
  - Proteobacteria
    - Campylobacter
    - Enterobacterales
      - Enterobacteriaceae
        - Klebsiella
          - 'Klebsiella pneumoniae'
        - Salmonella
      - 'Proteus mirabilis'
      - 'Yersinia <bacteria>'
  - 'Terrabacteria group'
    - 'Actinobacteria <phylum>'
    - Chloroflexi
      - Anaerolineae
        - Anaerolineales
          - Anaerolineaceae
    - Firmicutes

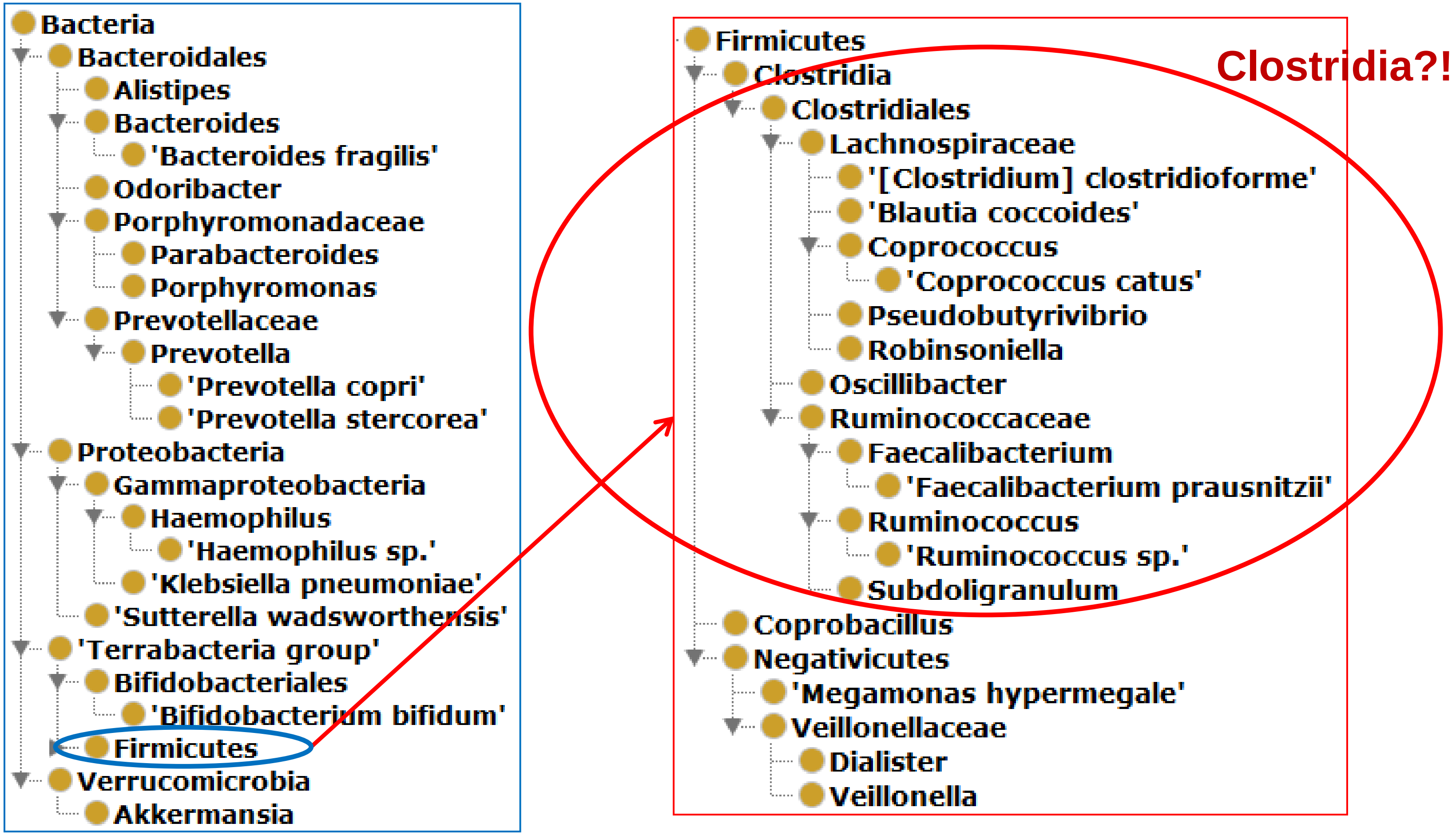
- Bacteroidetes
  - Bacteroidia
    - Bacteroidales
      - Bacteroidaceae
        - Bacteroides
          - 'Bacteroides plebeius'
          - 'Bacteroides sp.'
      - Porphyromonadaceae
        - Porphyromonas
          - 'Porphyromonas gingivalis'
          - 'Porphyromonas macacae'
      - Prevotellaceae
        - Prevotella
          - 'Prevotella copri'
      - Rikenellaceae

- 'Actinobacteria <phylum>'
  - 'Actinobacteria <class>'
    - Bifidobacterium
      - 'Bifidobacterium dentium'
    - Corynebacteriales
      - Nocardiaceae
        - 'Rhodococcus <Bacteria>'
  - Coriobacteriia
    - 'Collinsella aerofaciens'
    - Eggerthellaceae
      - Eggerthella
        - 'Eggerthella lenta'
      - 'Gordonibacter pamelaeae'

- Firmicutes
  - Clostridia
    - Clostridiales
      - 'Clostridium perfringens'
      - Eubacterium
      - Flavonifractor
      - Lachnospiraceae
        - '[Clostridium] asparagiforme'
        - 'Lachnospiraceae bacterium'
      - Ruminococcaceae
        - 'Ruminococcus lactaris'
  - Lactobacillales
    - Enterococcaceae
      - Enterococcus
    - 'Lactobacillus sp.'
    - Streptococcus
  - Negativicutes
    - Selenomonadales
    - Veillonellaceae
  - Turicibacter

Which bacteria are good for treatments?

- Clue: Bacteria decreased in guts:



- Bacteria
  - Bacteroidales
    - Alistipes
    - Bacteroides
      - 'Bacteroides fragilis'
    - Odoribacter
    - Porphyromonadaceae
      - Parabacteroides
      - Porphyromonas
    - Prevotellaceae
      - Prevotella
        - 'Prevotella copri'
        - 'Prevotella stercorea'
  - Proteobacteria
    - Gammaproteobacteria
      - Haemophilus
        - 'Haemophilus sp.'
      - 'Klebsiella pneumoniae'
    - 'Sutterella wadsworthensis'
  - 'Terrabacteria group'
    - Bifidobacteriales
      - 'Bifidobacterium bifidum'
    - Firmicutes
  - Verrucomicrobia
    - Akkermansia

- Firmicutes
  - Clostridia
    - Clostridiales
      - Lachnospiraceae
        - '[Clostridium] clostridioforme'
        - 'Blautia coccoides'
        - Coprococcus
          - 'Coprococcus catus'
        - Pseudobutyrivibrio
        - Robinsoniella
      - Oscillibacter
      - Ruminococcaceae
        - Faecalibacterium
          - 'Faecalibacterium prausnitzii'
        - Ruminococcus
          - 'Ruminococcus sp.'
        - Subdoligranulum
  - Coprobacillus
  - Negativicutes
    - 'Megamonas hypermegale'
    - Veillonellaceae
      - Dialister
      - Veillonella

Clostridia?!

Compared to increased bacteria: Same vs different …!

Summary and Discussion

- OHMI represents, standardizes, and integrates terminologies and data/metadata in the domain of host-microbiome interactions

- OHMI is applied in many use cases, helps rheumatic disease HMI studies

- *Discussion*: What's next?

Acknowledgements

University of Michigan

- Haihe Wang
- Hong Yu
- Jiahao Wang
- Yongqun “Oliver” He

Duke

- Anna Maria Masci

UPenn

- Jie Zheng
- Daniel P. Beiting

MUSC

- Jihad S. Obeid
- Alexander V. Alekseyenko

Funding:

- Harbin University travel fund to Dr. Wang
- College of Medicine Enhancing Team Science (COMETS) award to Dr. Alekseyenko