Using Data and Analytics to Unlock the Microbiome Impact on Human Health

世良　実穂
Clarivate Analytics
シニアコンサルタント

Cortellis
Powering Life Sciences Innovation

Clarivate
Analytics

Alexander Ivliev, Ph.D.
Director, Informatics, Discovery and Translational Services

Clarivate Analytics

Who is Clarivate?

Metabase

- Largest manually curated database of protein, RNA, drug and metabolite interactions;
- Available for human, mouse and rat;
- Comes with a versatile toolkit of methods for network analysis

Metacore

- User interface to Metabase with integrated pathway analysis workflows for diverse OMICs datasets;
- More than 1600 richly annotated pathway maps for results visualisation

Integrity

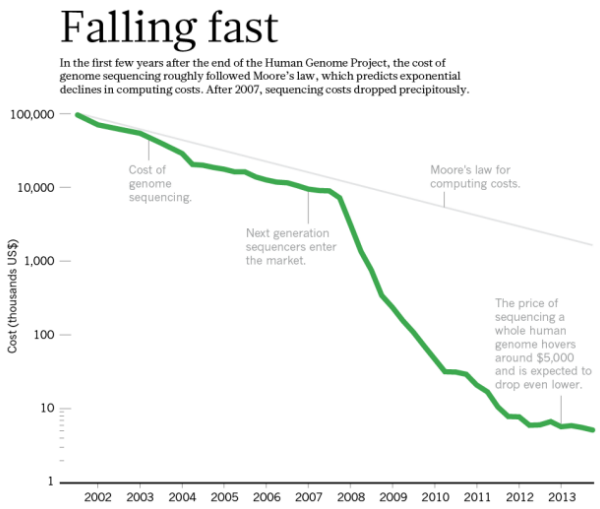
- Compound-target database containing over 450 000 compounds with biological activity;
- Supported by data on pharmacology, PK, experimental models, patents, clinical studies, etc.

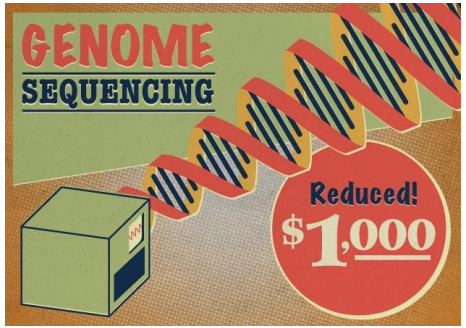
Cortellis

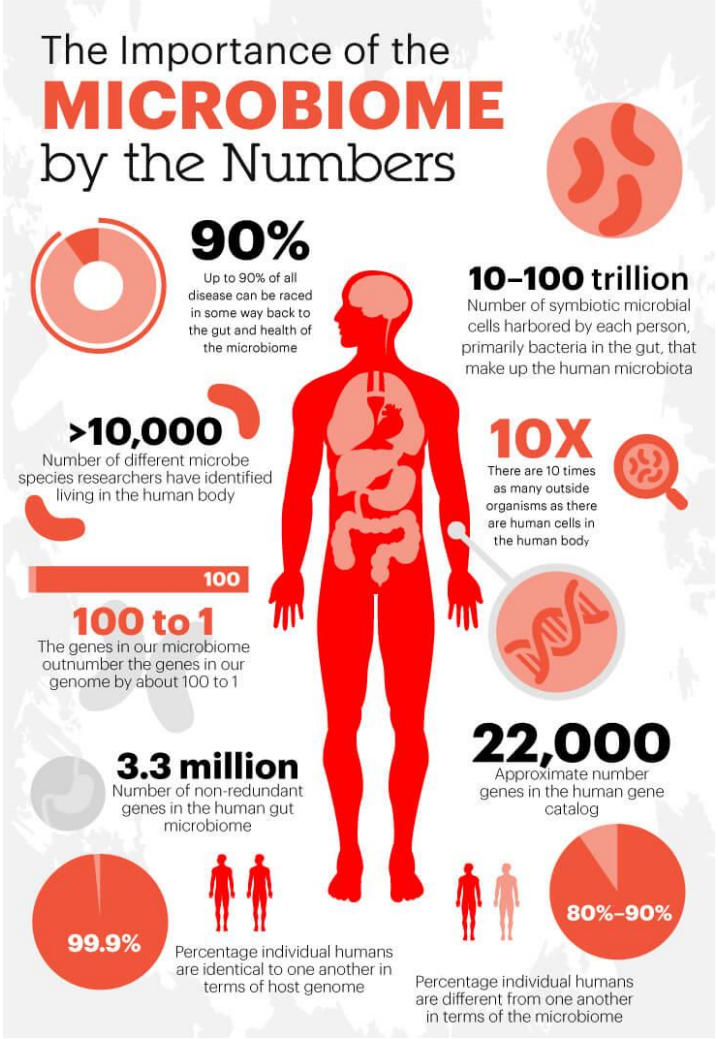
- Suite of intelligence solution for late stages of drug development;
- Provides intelligence in Drug Pipeline, Clinical Trial and Regulatory areas

Clarivate Analytics

Why Microbiome







https://draxe.com/microbiome/

Clarivate Analytics

Clarivate Analytics' Solutions in the Microbiome Space

1. Manual curation of microbial pathways and host-microbial interactions from publications
2. Curation and harmonization of public datasets for large-scale meta-analyses
3. Bioinformatics services and custom end-to-end software development

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Pathway Curation – MetaMiner Partnerships

Completed

Cystic Fibrosis
CFF Foundation

Asthma

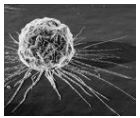
AZ, JNJ, Merck

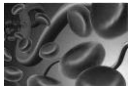
Prostate Cancer

Exclusive Project

Multiple Sclerosis

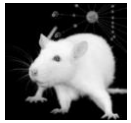
Vertex, IOP

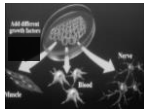
Oncology

Eli Lilly
Millennium
J&J
Tgen
Van Andel
Harvard
Johns Hopkins
CRUK

Hematology

Exclusive Project

Immunology

Celgene, BI

Toxicology

Elan
FDA
Vertex

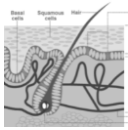
Stem Cells

Astra Zeneca
Eli Lilly
Novartis
Chicago Children's Hospital
University of Glasgow
University of Sheffield
University of Queensland
USC

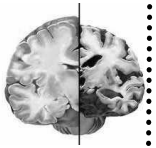
Dry Eye

Exclusive Project

Depression

Vertex, IOP

Dermatitis

Unilever

Huntington's

CHDI

Diabetes, Obesity, Metabolic Syndrome

Eli Lilly
TNO
FDA
University of Amsterdam

COPD

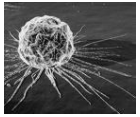
AZ

Neurofibromatosis

Children's Tumor Foundation

Eye Diseases

Novartis

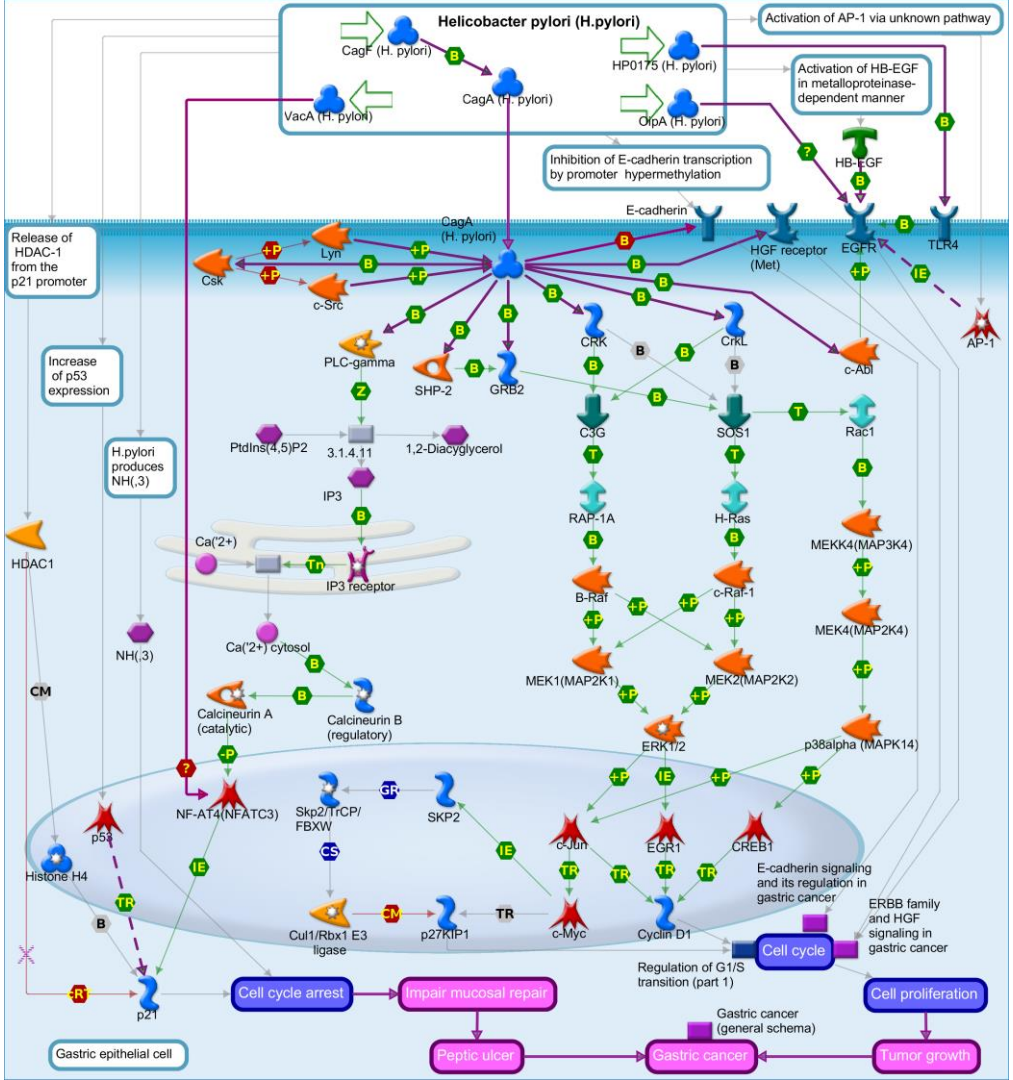
Immuno Oncology

3 large Pharma
1 small Pharma

Coming soon

Microbiome


Drug combinations


Clarivate Analytics



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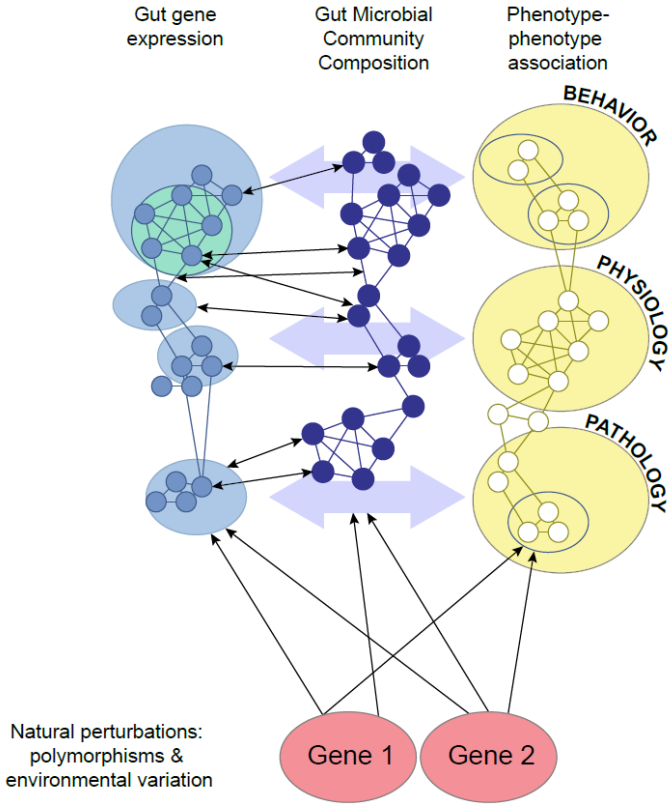
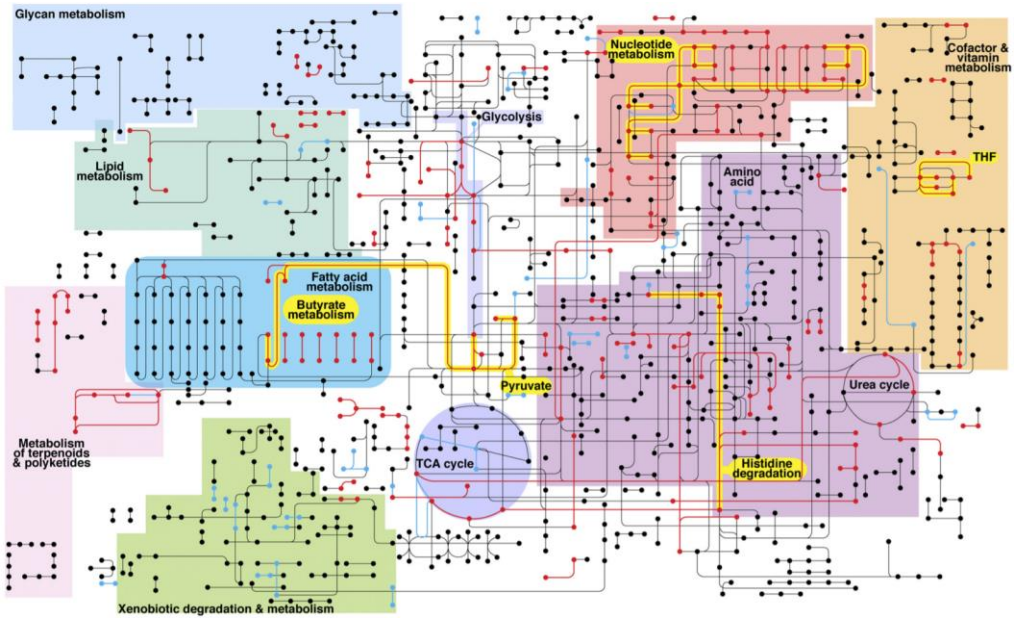
Microbiome-Host Modelling Challenges

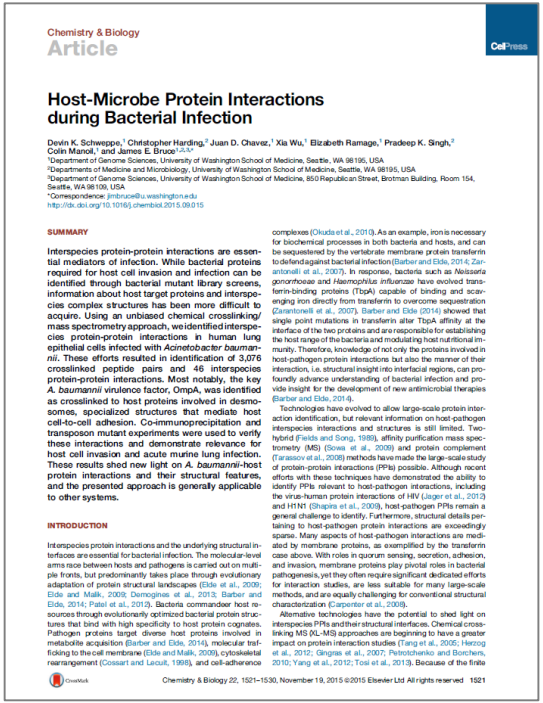




Clarivate Analytics

Database of Microbial-Host Interactions (DoMI) – Article Examples

Protein-protein interactions



Chemistry & Biology
Article

Host-Microbe Protein Interactions during Bacterial Infection

Devin K. Schweppe,[1] Christopher Harding,[2] Juan D. Chavez,[1] Xia Wu,[1] Elizabeth Ramage,[1] Pradeep K. Singh,[2] Colin Manoil,[1] and James E. Bruce[1,3,*]
[1]Department of Genome Sciences, University of Washington School of Medicine, Seattle, WA 98195, USA
[2]Departments of Medicine and Microbiology, University of Washington School of Medicine, Seattle, WA 98195, USA
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http://dx.doi.org/10.1016/j.chembiol.2015.09.015

SUMMARY

Interspecies protein-protein interactions are essential mediators of infection. While bacterial proteins required for host cell invasion and infection can be identified through bacterial mutant library screens, information about host target proteins and interspecies complex structures has been more difficult to acquire. Using an unbiased chemical crosslinking/mass spectrometry approach, we identified interspecies protein-protein interactions in human lung epithelial cells infected with *Acinetobacter baumannii*. These efforts resulted in identification of 3,076 crosslinked peptide pairs and 46 interspecies protein-protein interactions. Most notably, the key *A. baumannii* virulence factor, OmpA, was identified as crosslinked to host proteins involved in desmosomes, specialized structures that mediate host cell-to-cell adhesion. Co-immunoprecipitation and transposon mutant experiments were used to verify these interactions and demonstrate relevance for host cell invasion and acute murine lung infection. These results shed new light on *A. baumannii*-host protein interactions and their structural features, and the presented approach is generally applicable to other systems.

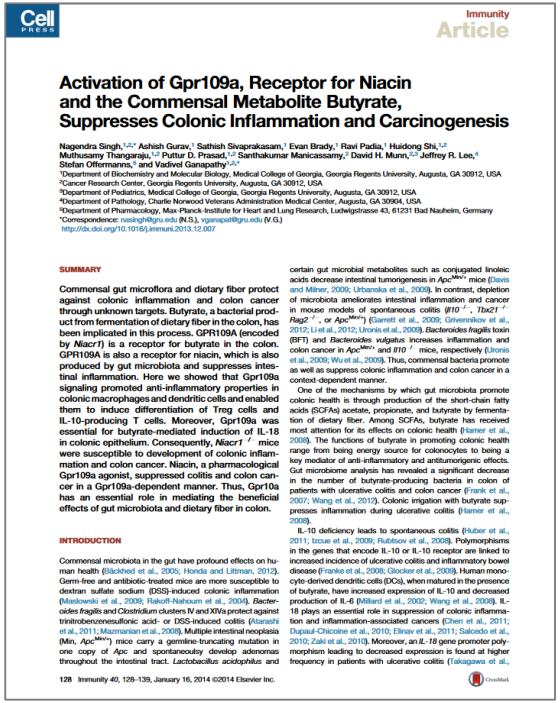
INTRODUCTION

Interspecies protein interactions and the underlying structural interfaces are essential for bacterial infection. The molecular-level arms race between hosts and pathogens is carried out on multiple fronts, but predominantly takes place through evolutionary adaptation of protein structural landscapes (Elde et al., 2009; Elde and Malik, 2009; Damociginas et al., 2013; Barber and Elde, 2014; Patel et al., 2012). Bacteria commandeer host resources through evolutionarily optimized bacterial protein structures that bind with high specificity to host protein cognates. Pathogen proteins target diverse host proteins involved in metabolite acquisition (Barber and Elde, 2014), molecular trafficking to the cell membrane (Elde and Malik, 2009), cytoskeletal rearrangement (Cossart and Lecuit, 1998), and cell-adherence complexes (Okuda et al., 2010). As an example, iron is necessary for biochemical processes in both bacteria and hosts, and can be sequestered by the vertebrate membrane protein transferrin to defend against bacterial infection (Barber and Elde, 2014; Zaritsonelli et al., 2007). In response, bacteria such as *Neisseria gonorrhoeae* and *Haemophilus influenzae* have evolved transferrin-binding proteins (TbpA) capable of binding and scavenging iron directly from transferrin to overcome sequestration (Zarantonelli et al., 2007). Barber and Elde (2014) showed that single point mutations in transferrin alter TbpA affinity at the interface of the two proteins and are responsible for establishing the host range of the bacteria and modulating host nutritional immunity. Therefore, knowledge of not only the proteins involved in host-pathogen protein interactions but also the manner of their interaction, i.e. structural insight into interfacial regions, can profoundly advance understanding of bacterial infection and provide insight for the development of new antimicrobial therapies (Barber and Elde, 2014).

Technologies have evolved to allow large-scale protein interaction identification, but relevant information on host-pathogen interspecies interactions and structures is still limited. Two-hybrid (Fields and Song, 1989), affinity purification mass spectrometry (MS) (Sowa et al., 2009) and protein complement (Tarassov et al., 2008) methods have made the large-scale study of protein-protein interactions (PPIs) possible. Although recent efforts with these techniques have demonstrated the ability to identify PPIs relevant to host-pathogen interactions, including the virus-human protein interactions of HIV (Jäger et al., 2012) and H1N1 (Shapira et al., 2009), host-pathogen PPIs remain a general challenge to identify. Furthermore, structural details pertaining to host-pathogen protein interactions are exceedingly sparse. Many aspects of host-pathogen interactions are mediated by membrane proteins, as exemplified by the transferrin case above. With roles in quorum sensing, secretion, adhesion, and invasion, membrane proteins play pivotal roles in bacterial pathogenesis, yet they often require significant dedicated efforts for interaction studies, are less suitable for many large-scale methods, and are equally challenging for conventional structural characterization (Carpenter et al., 2008).

Alternative technologies have the potential to shed light on interspecies PPIs and their structural interfaces. Chemical crosslinking MS (XL-MS) approaches are beginning to have a greater impact on protein interaction studies (Tang et al., 2005; Herzog et al., 2012; Gingras et al., 2007; Petrotchenko and Borchers, 2010; Yang et al., 2012; Tosi et al., 2013). Because of the finite

Metabolite-protein interactions



Cell PRESS
Immunity
Article

Activation of Gpr109a, Receptor for Niacin and the Commensal Metabolite Butyrate, Suppresses Colonic Inflammation and Carcinogenesis

Nagendra Singh,[1,2,*] Ashish Gurav,[1] Sathish Sivaprakasam,[1] Evan Brady,[1] Ravi Padia,[1] Huidong Shi,[1,2] Muthusamy Thangaraju,[1,3] Puttur D. Prasad,[1,2] Santhakumar Manicassamy,[2] David H. Munn,[2,3] Jeffrey R. Lee,[4] Stefan Offermanns,[5] and Vadivel Ganapathy[1,2,*]
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http://dx.doi.org/10.1016/j.immuni.2013.12.007

SUMMARY

Commensal gut microflora and dietary fiber protect against colonic inflammation and colon cancer through unknown targets. Butyrate, a bacterial product from fermentation of dietary fiber in the colon, has been implicated in this process. GPR109A (encoded by *Niacr1*) is a receptor for butyrate in the colon. GPR109A is also a receptor for niacin, which is also produced by gut microbiota and suppresses intestinal inflammation. Here we showed that Gpr109a signaling promoted anti-inflammatory properties in colonic macrophages and dendritic cells and enabled them to induce differentiation of Treg cells and IL-10-producing T cells. Moreover, Gpr109a was essential for butyrate-mediated induction of IL-18 in colonic epithelium. Consequently, *Niacr1*$^{-/-}$ mice were susceptible to development of colonic inflammation and colon cancer. Niacin, a pharmacological Gpr109a agonist, suppressed colitis and colon cancer in a Gpr109a-dependent manner. Thus, Gpr10a has an essential role in mediating the beneficial effects of gut microbiota and dietary fiber in colon.

INTRODUCTION

Commensal microbiota in the gut have profound effects on human health (Bäckhed et al., 2005; Honda and Littman, 2012). Germ-free and antibiotic-treated mice are more susceptible to dextran sulfate sodium (DSS)-induced colonic inflammation (Maslowski et al., 2009; Rakoff-Nahoum et al., 2004). *Bacteroides fragilis* and *Clostridium* clusters IV and XIVa protect against trinitrobenzenesulfonic acid- or DSS-induced colitis (Atarashi et al., 2011; Mazmanian et al., 2008). Multiple intestinal neoplasia (Min, *Apc*$^{Min/+}$) mice carry a germline-truncating mutation in one copy of *Apc* and spontaneously develop adenomas throughout the intestinal tract. *Lactobacillus acidophilus* and certain gut microbial metabolites such as conjugated linoleic acids decrease intestinal tumorigenesis in *Apc*$^{Min/+}$ mice (Davis and Milner, 2009; Urbanska et al., 2009). In contrast, depletion of microbiota ameliorates intestinal inflammation and cancer in mouse models of spontaneous colitis (*Il10*$^{-/-}$, *Tbx21*$^{-/-}$ *Rag2*$^{-/-}$, or *Apc*$^{Min/+}$) (Garrett et al., 2009; Grivennikov et al., 2012; Li et al., 2012; Uronis et al., 2009). *Bacteroides fragilis* toxin (BFT) and *Bacteroides vulgatus* increases inflammation and colon cancer in *Apc*$^{Min/+}$ and *Il10*$^{-/-}$ mice, respectively (Uronis et al., 2009; Wu et al., 2009). Thus, commensal bacteria promote as well as suppress colonic inflammation and colon cancer in a context-dependent manner.

One of the mechanisms by which gut microbiota promote colonic health is through production of the short-chain fatty acids (SCFAs) acetate, propionate, and butyrate by fermentation of dietary fiber. Among SCFAs, butyrate has received most attention for its effects on colonic health (Hamer et al., 2008). The functions of butyrate in promoting colonic health range from being energy source for colonocytes to being a key mediator of anti-inflammatory and antitumorigenic effects. Gut microbiome analysis has revealed a significant decrease in the number of butyrate-producing bacteria in colon of patients with ulcerative colitis and colon cancer (Frank et al., 2007; Wang et al., 2012). Colonic irrigation with butyrate suppresses inflammation during ulcerative colitis (Hamer et al., 2008).

IL-10 deficiency leads to spontaneous colitis (Huber et al., 2011; Izcue et al., 2009; Rubtsov et al., 2008). Polymorphisms in the genes that encode IL-10 or IL-10 receptor are linked to increased incidence of ulcerative colitis and inflammatory bowel disease (Franke et al., 2008; Glocker et al., 2009). Human monocyte-derived dendritic cells (DCs), when matured in the presence of butyrate, have increased expression of IL-10 and decreased production of IL-6 (Millard et al., 2002; Wang et al., 2009). IL-18 plays an essential role in suppression of colonic inflammation and inflammation-associated cancers (Chen et al., 2011; Dupaul-Chicoine et al., 2010; Elinav et al., 2011; Salcedo et al., 2010; Zaki et al., 2010). Moreover, an *IL-18* gene promoter polymorphism leading to decreased expression is found at higher frequency in patients with ulcerative colitis (Takagawa et al.,

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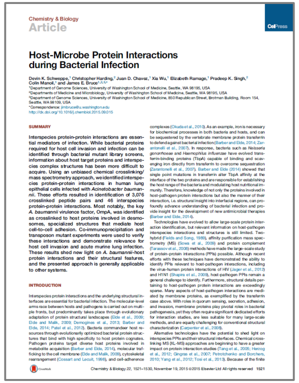
Database of Microbial-Host Interactions (DoMI) – Literature Annotation Data Elements



Chemistry & Biology
Article
CellPress

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Fields for annotation (protein-protein interactions):

- PubMed ID
- Protein names & IDs
- Gene names & IDs
- Organisms, including species and strain
- Interaction detection method
- Host system (tissue/cell line)
- Type/mechanism of interaction (e.g. binding, transcription regulation, influence on expression)
- Effect of interaction (i.e. activation, inhibition, unknown)
- Confidence (interaction reliability based on interaction types and detection methods)

- **Controlled vocabularies**
- **IDs**
- **Metadata**

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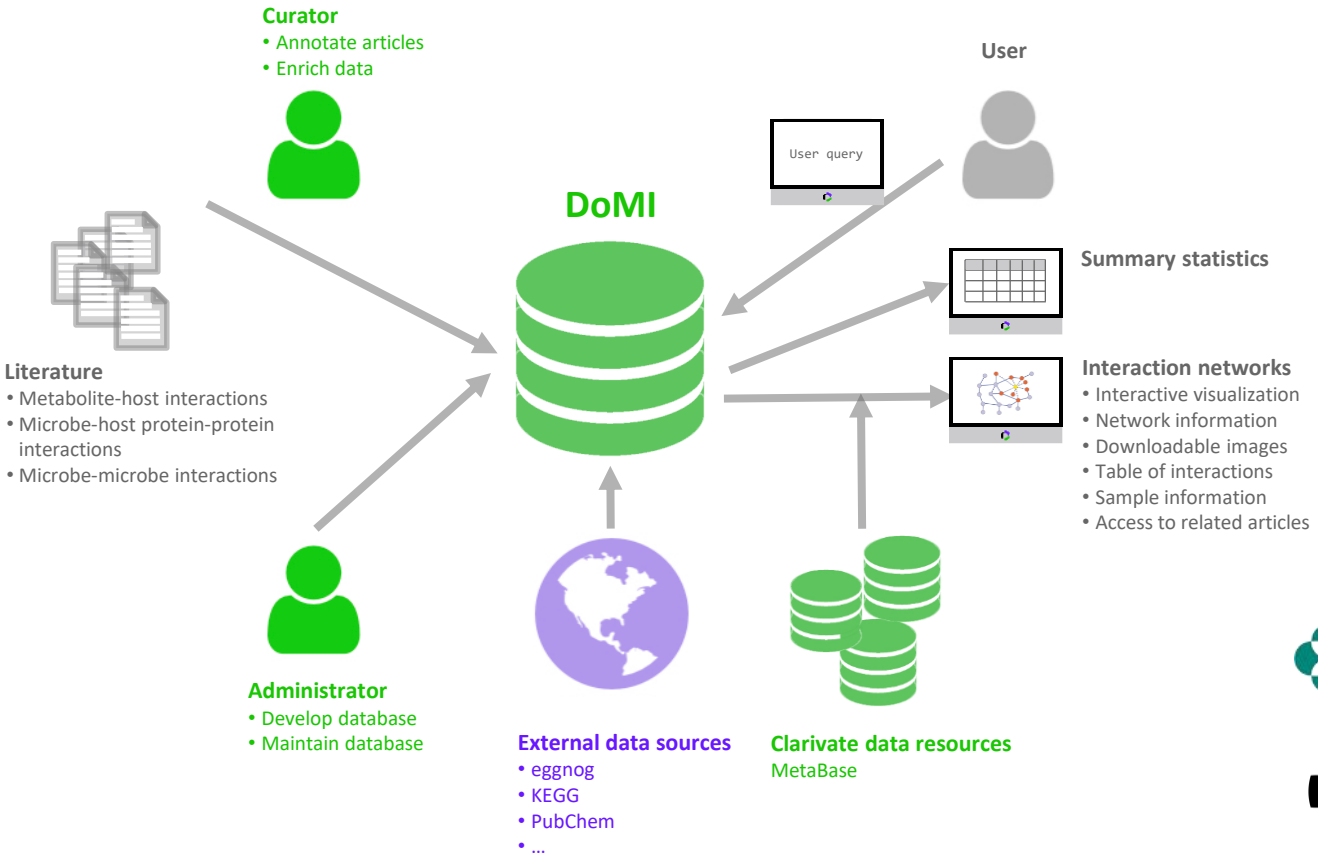
Database of Microbial-Host Interactions (DoMI)



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Clarivate Analytics' Solutions in the Microbiome Space

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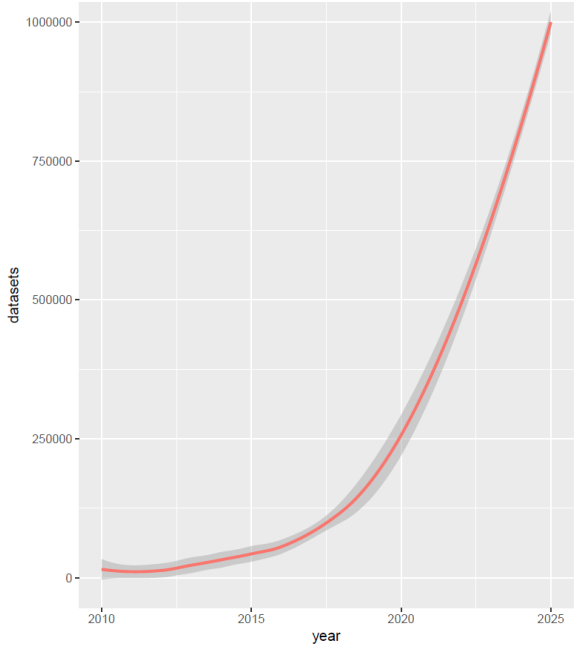
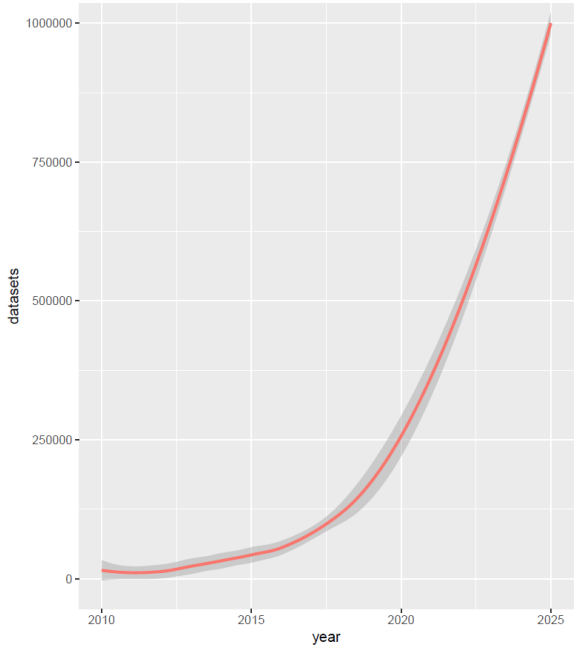
2. Curation and harmonization of public datasets for large-scale meta-analyses
3. Bioinformatics services and custom end-to-end software development



What's the Problem with This?

1. Lack of consistent terminology
2. Scarce meta-data: critical information is often only contained in paper full texts



~2,000 BioProjects and ~250,000 Samples: Comprehensive Human Gut Microbiome Study Set

Programmatic text mining

Manual literature curation

Study level

- Biomes diversity
  - Human
  - Stool
- Including large-scale projects (HMP, MetaHIT)
- Disease
  - Healthy
- Major public data repositories (NCBI, EMBL-EBI)
- Number of samples
- Center name
  - Platform
  - Number of runs
- Data size
- Submission date
  - Analysis status
- Publications
  - Title
  - Authors
  - PubMed ID
- Study design
  - Cross-sectional
  - Longitudinal
- Experimental methods
  - Collection
  - Extraction
- Bioinformatics analysis workflows
- Host/microbiome additional data
  - Transcriptomics
  - Proteomics
  - Metabolomics

Sample level

- Sample identification
  - Name
  - Sample ID
  - Subject ID
  - Project name
- Traceability
  - Collection date
  - Geographic location
  - Body site
- Host
  - Age
  - Gender
  - Ethnicity
  - Disease
- Sequencing
  - Library source
  - Platform
  - Single/paired end
  - Read length
  - Number of reads
- Biome
  - Organism
  - Material
  - Features
- Sequence of focus:
  - Amplicon variable region
- Genotype information (yes/no)
- Sample source
  - Stool
  - Intestinal biopsy
  - Intestine region
- Disease details
  - Disease subtypes
  - Active/inactive, etc

Custom project for a pharmaceutical company client

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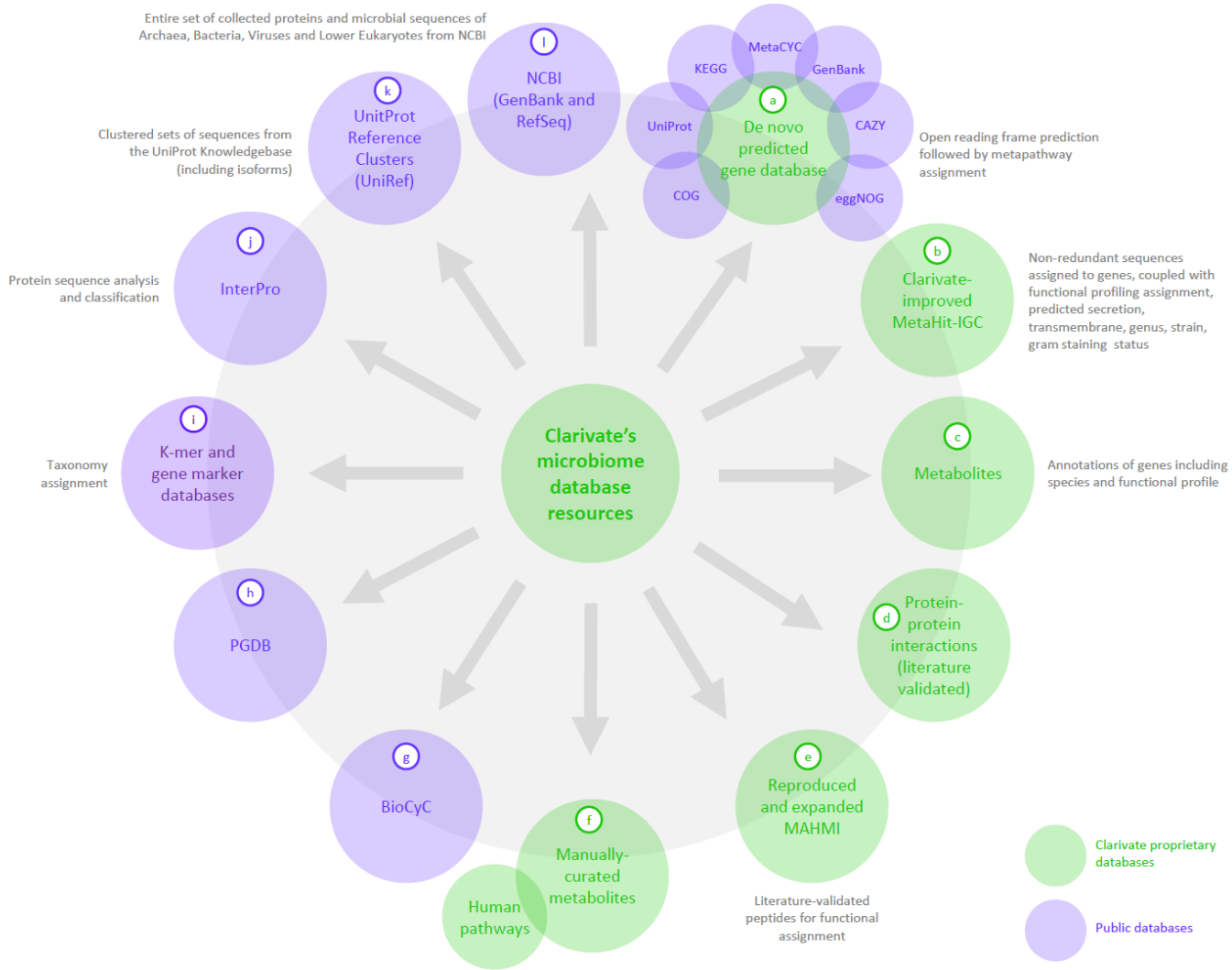
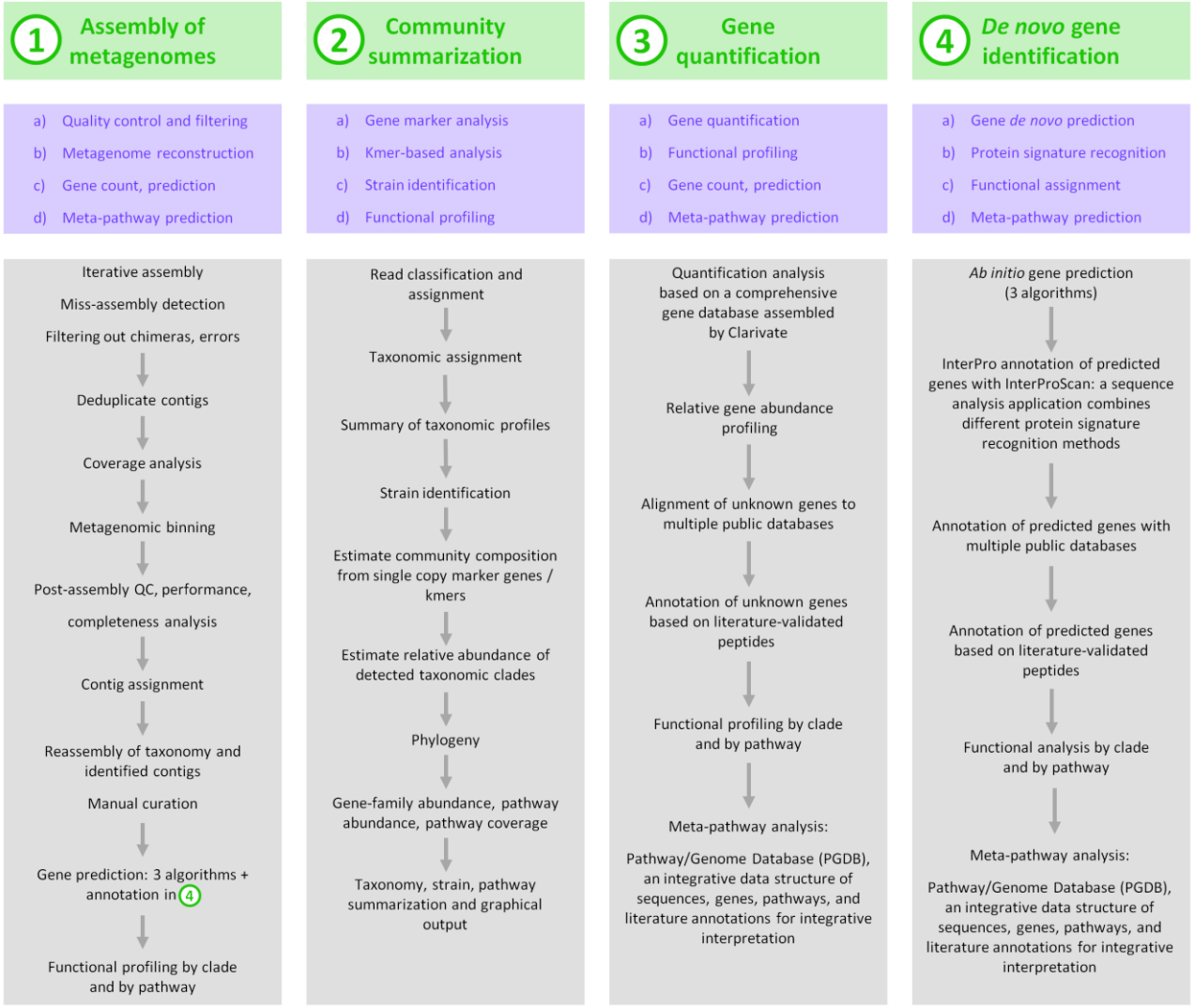
1. Manual curation of microbial pathways and host-microbial interactions from publications
2. Curation and harmonization of public datasets for large-scale meta-analyses
3. Bioinformatics services and custom end-to-end software development


Entire set of collected proteins and microbial sequences of Archaea, Bacteria, Viruses and Lower Eukaryotes from NCBI
l
NCBI (GenBank and RefSeq)
k
UnitProt Reference Clusters (UniRef)
Clustered sets of sequences from the UniProt Knowledgebase (including isoforms)
j
InterPro
Protein sequence analysis and classification
i
K-mer and gene marker databases
Taxonomy assignment
h
PGDB
g
BioCyC
Human pathways
f
Manually-curated metabolites
e
Reproduced and expanded MAHMI
Literature-validated peptides for functional assignment
d
Protein-protein interactions (literature validated)
c
Metabolites
Annotations of genes including species and functional profile
b
Clarivate-improved MetaHit-IGC
Non-redundant sequences assigned to genes, coupled with functional profiling assignment, predicted secretion, transmembrane, genus, strain, gram staining status
a
De novo predicted gene database
MetaCYC
KEGG
GenBank
UniProt
CAZY
COG
eggNOG
Open reading frame prediction followed by metapathway assignment
Clarivate's microbiome database resources
Clarivate proprietary databases
Public databases


1 Assembly of metagenomes
a) Quality control and filtering
b) Metagenome reconstruction
c) Gene count, prediction
d) Meta-pathway prediction
Iterative assembly
Miss-assembly detection
Filtering out chimeras, errors
Deduplicate contigs
Coverage analysis
Metagenomic binning
Post-assembly QC, performance, completeness analysis
Contig assignment
Reassembly of taxonomy and identified contigs
Manual curation
Gene prediction: 3 algorithms + annotation in 4
Functional profiling by clade and by pathway
2 Community summarization
a) Gene marker analysis
b) Kmer-based analysis
c) Strain identification
d) Functional profiling
Read classification and assignment
Taxonomic assignment
Summary of taxonomic profiles
Strain identification
Estimate community composition from single copy marker genes / kmers
Estimate relative abundance of detected taxonomic clades
Phylogeny
Gene-family abundance, pathway abundance, pathway coverage
Taxonomy, strain, pathway summarization and graphical output
3 Gene quantification
a) Gene quantification
b) Functional profiling
c) Gene count, prediction
d) Meta-pathway prediction
Quantification analysis based on a comprehensive gene database assembled by Clarivate
Relative gene abundance profiling
Alignment of unknown genes to multiple public databases
Annotation of unknown genes based on literature-validated peptides
Functional profiling by clade and by pathway
Meta-pathway analysis:
Pathway/Genome Database (PGDB), an integrative data structure of sequences, genes, pathways, and literature annotations for integrative interpretation
4 De novo gene identification
a) Gene de novo prediction
b) Protein signature recognition
c) Functional assignment
d) Meta-pathway prediction
Ab initio gene prediction (3 algorithms)
InterPro annotation of predicted genes with InterProScan: a sequence analysis application combines different protein signature recognition methods
Annotation of predicted genes with multiple public databases
Annotation of predicted genes based on literature-validated peptides
Functional analysis by clade and by pathway
Meta-pathway analysis:
Pathway/Genome Database (PGDB), an integrative data structure of sequences, genes, pathways, and literature annotations for integrative interpretation

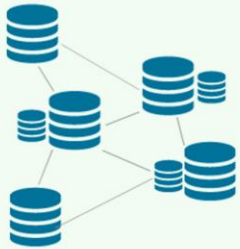
Cases of Bioinformatics Projects

- Target molecules identification
- Target disease prioritization
- Reconstruction of drug MoA
- Drug repositioning
- Patient stratificatioin
- Concomitant drug identification
- Cell type prediction
- Microbiome

Clarivate Analytics

Your Objectives → Define and Design → Implementation

Database Development



Data Integration

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