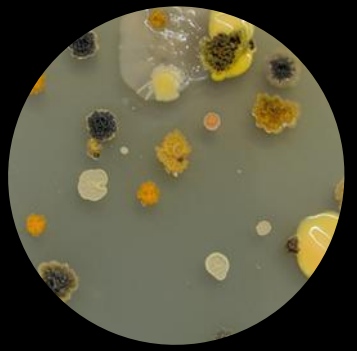
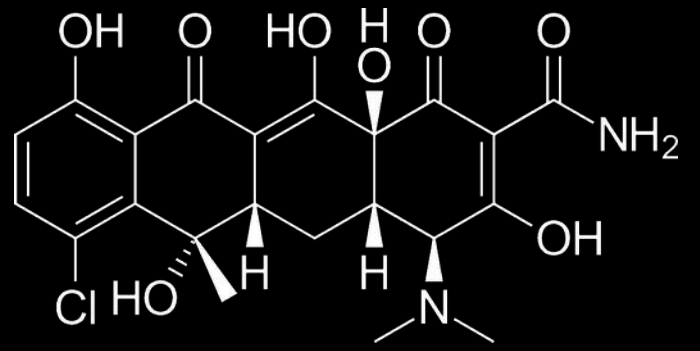
Information-rich platforms for natural product antibiotic drug discovery and microbial characterization

Chase Clark
Postdoctoral Research Associate
Computation and Informatics in Biology and Medicine Training Program
Jason Kwan Lab
School of Pharmacy
University of Wisconsin-Madison

IDBac





SocialGene

GTGGAGGAGCAG
CGGGCCGGGAGC
CG.....

Education:

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Ph.D. in Pharmacognosy from UIC (F31)

Current:

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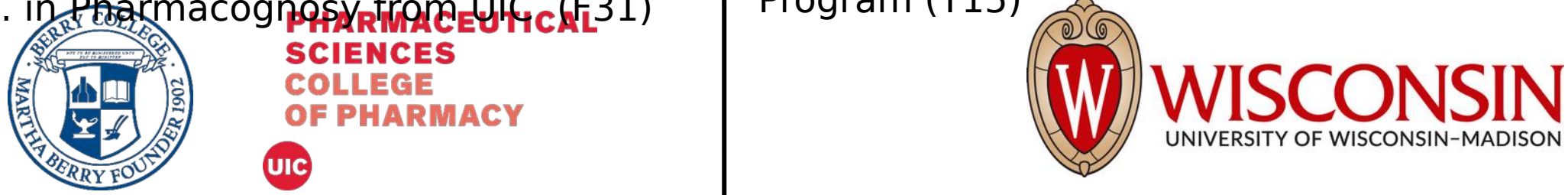
Computation and Informatics in Biology and Medicine Program (T15)



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WISCONSIN
UNIVERSITY OF WISCONSIN–MADISON

Previous:

Deerland
Probiotics & Enzymes

Head of Method Development

Enzyme USP / FCC assays
HPLC analysis
Bioavailability testing
FTIR/Raman identity testing of raw materials
Preservatives, Allergens, Western Blot testing capabilities
Application development / formulation support

R&D Tech

- New product development
- Technical support for sales team
- Troubleshooting QC and production/manufacturing

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“Drugs”
“Natural Products”
“Specialized Metabolites”

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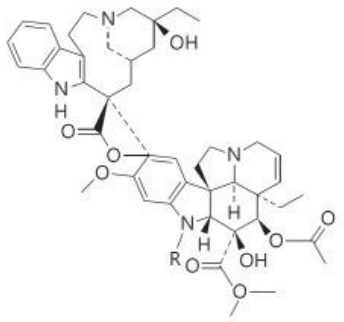
“Natural Products”
“Specialized Metabolites”

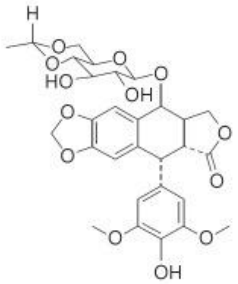
Over 60% of current anticancer drugs are
derived in one way or another from natural sources

Cragg, Gordon M, and John M Pezzuto. “Natural Products as a Vital Source for the Discovery of Cancer Chemotherapeutic and Chemopreventive Agents.” *Medical principles and practice : international journal of the Kuwait University, Health Science Centre* vol. 25 Suppl 2,Suppl 2 (2016): 41-59. doi:10.1159/000443404

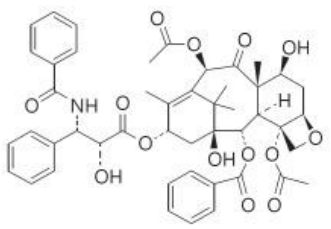
“Natural Products”



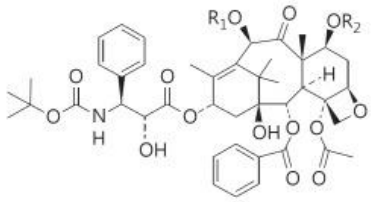
1 VBL R = CH_3
2 VCR R = CHO



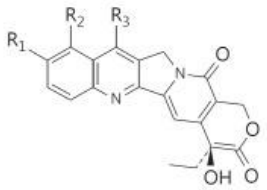
3 Etoposide



4 Paclitaxel (Taxol™)

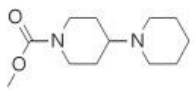


5 Docetaxel (Taxotere™) $R_1 = R_2 = H$
6 Cabazitaxel $R_1 = R_2 = CH_3$



7 CPT $R_1 = R_2 = R_3 = H$
8 Topotecan $R_1 = OH$; $R_2 = CH_2NH(CH_3)_2$; $R_3 = H$

9 Irinotecan R_1 =



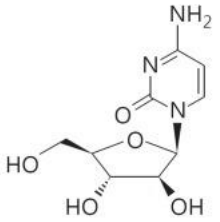
$R_2 = H$
$R_3 = CH_2CH_3$

10 Belotecan $R_1 = R_2 = H$; $R_3 = (CH_2)_2NHCH(CH_3)_2$
11 Cositecan $R_1 = R_2 = H$; $R_3 = (CH_2)_2Si(CH_3)_3$
12 SN-38 $R_1 = OH$; $R_2 = H$; $R_3 = CH_2CH_3$

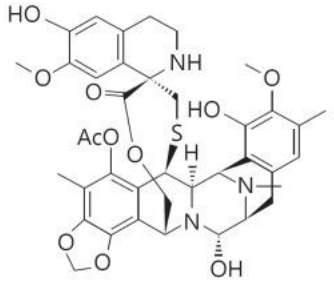
Natural products from plants

- Cragg, Gordon M, and John M Pezzuto. “Natural Products as a Vital Source for the Discovery of Cancer Chemotherapeutic and Chemopreventive Agents.” *Medical principles and practice : international journal of the Kuwait University, Health Science Centre* vol. 25 Suppl 2,Suppl 2 (2016): 41-59. doi:10.1159/000443404
- Cragg, G M et al. “The taxol supply crisis. New NCI policies for handling the large-scale production of novel natural product anticancer and anti-HIV agents.” *Journal of natural products* vol. 56,10 (1993): 1657-68. doi:10.1021/np50100a001
- Stierle, A et al. “The search for a taxol-producing microorganism among the endophytic fungi of the Pacific yew, Taxus brevifolia.” *Journal of natural products* vol. 58,9 (1995): 1315-24. doi:10.1021/np50123a002

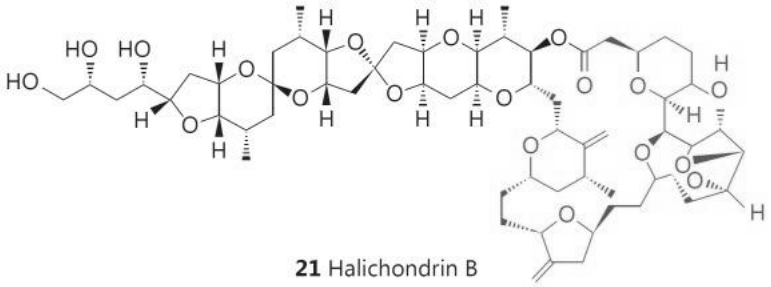
“Natural Products”



19 Cytarabine



20 Trabectedin (ET743; Yondelis®)



21 Halichondrin B

Natural products from marine organisms

Cragg, Gordon M, and John M Pezzuto. “Natural Products as a Vital Source for the Discovery of Cancer Chemotherapeutic and Chemopreventive Agents.” *Medical principles and practice : international journal of the Kuwait University, Health Science Centre* vol. 25 Suppl 2,Suppl 2 (2016): 41-59. doi:10.1159/000443404

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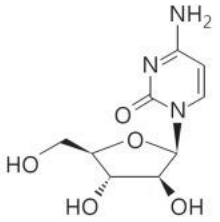

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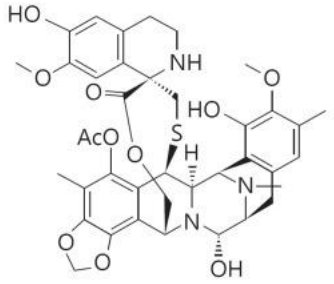

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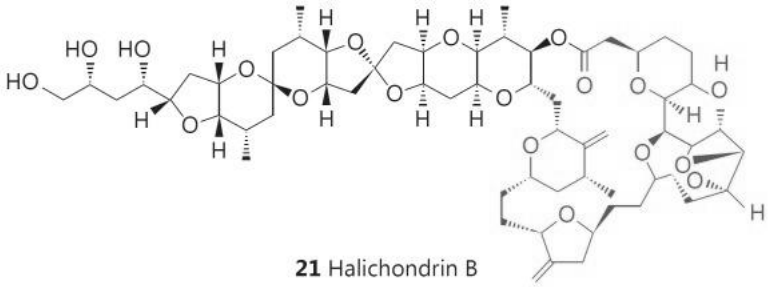

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Supply issue can be a huge problem

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The Threat of Antibiotic Resistance in the United States

Antibiotic resistance—when germs (bacteria, fungi) develop the ability to defeat the antibiotics designed to kill them—is one of the greatest global health challenges of modern time.

New National Estimate*

Each year, antibiotic-resistant bacteria and fungi cause at least an estimated:

2,868,700 infections

35,900 deaths

+

***Clostridioides difficile* is related to antibiotic use and antibiotic resistance:**

223,900 cases

12,800 deaths

New Antibiotic Resistance Threats List

Updated urgent, serious, and concerning threats—totaling 18

5 urgent threats

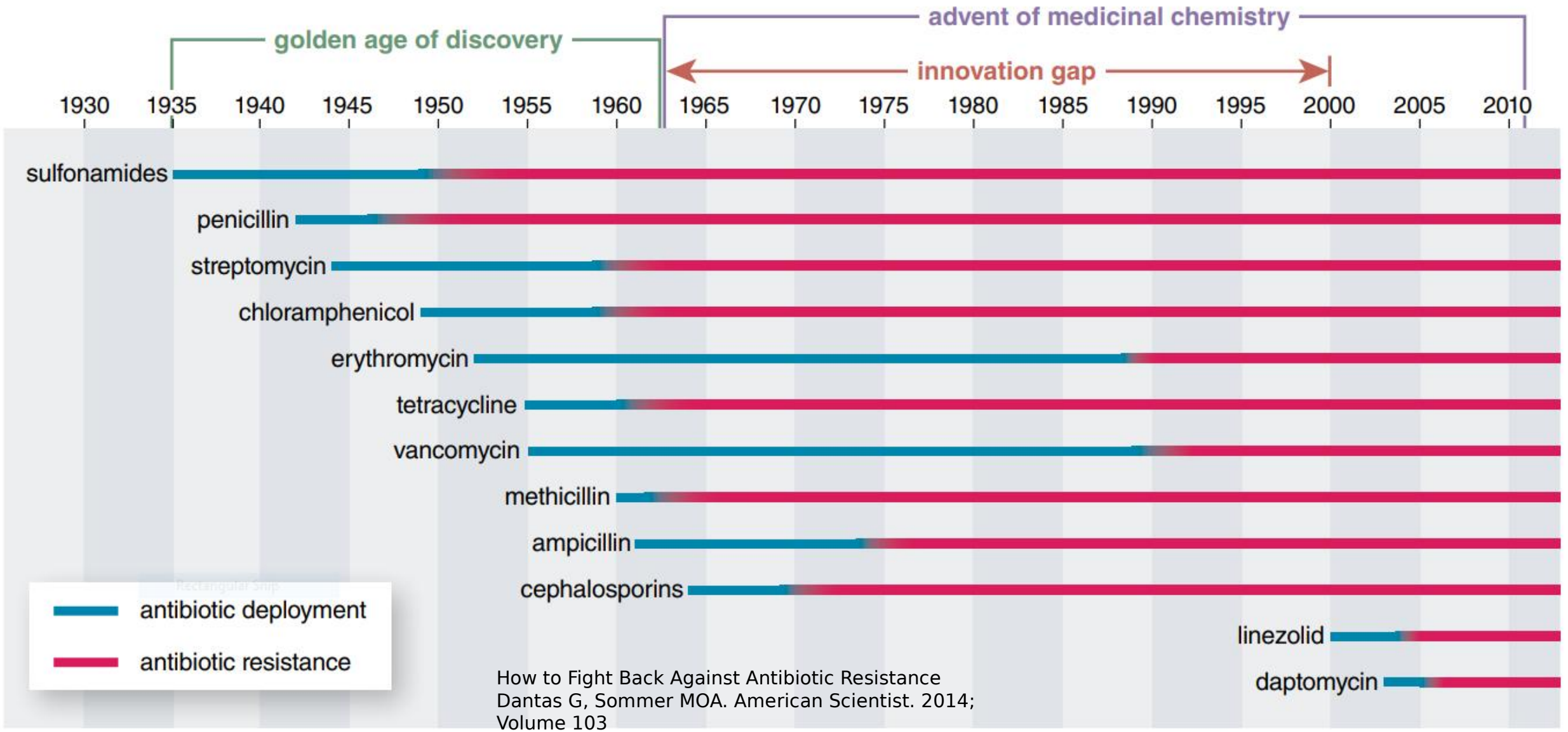
2 new threats

NEW: Watch List with **3** threats

Antibiotic resistance remains a significant One Health problem, affecting humans, animals, and the environment. Data show infection prevention and control is saving lives—especially in hospitals—but threats may undermine this progress without continued aggressive action now.

Learn more: www.cdc.gov/DrugResistance/Biggest-Threats

*National burden reflects de-duplicated infection and death estimates.



How to Fight Back Against Antibiotic Resistance
Dantas G, Sommer MOA. American Scientist. 2014;
Volume 103

Combinatorial Chemistry vs Natural Products

70 HTS campaigns
3 million compounds
19 Hits
5 Leads

65 HTS campaigns
2 million compounds
57 Hits
19 Leads

3 million compounds

____ Gram-negative antibiotics with cellular activity

Nat Rev Drug Discov **2007**, *6*, 29
Nat Rev Drug Discov **2015**, *14*, 529
J Med Chem **2014**, *57*, 10144

Slide from Professor Paul J. Hergenrother, UIUC, adapted with permission

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J Med Chem **2014**, *57*, 10144

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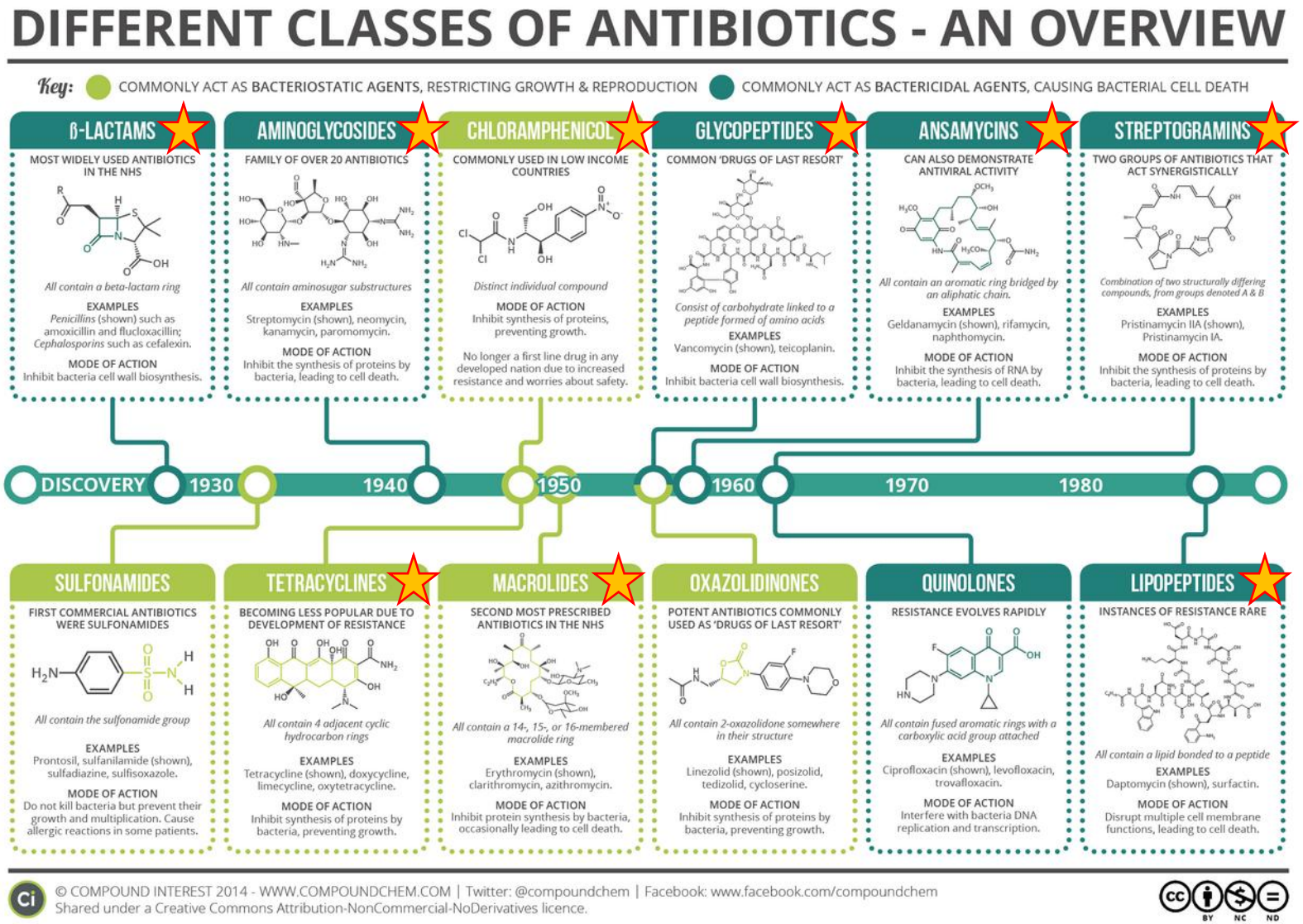
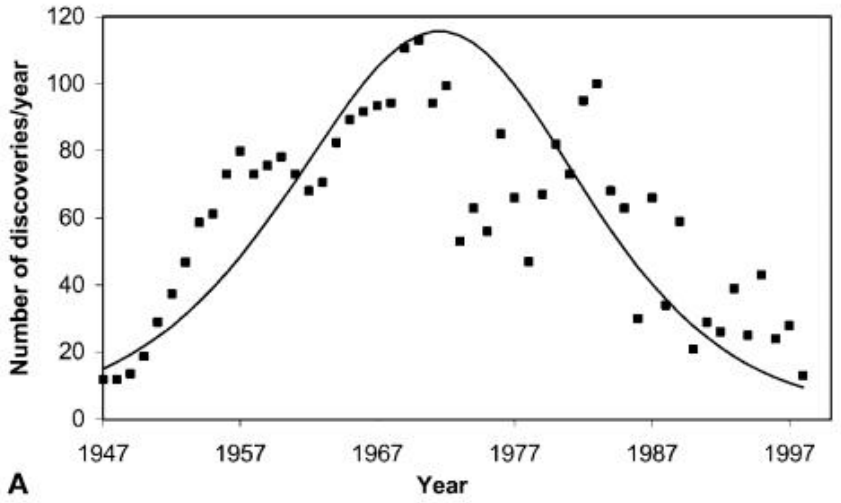
Bacteria (and fungi) as sources of antibiotics



Are there more compounds to find in *Streptomyces?*



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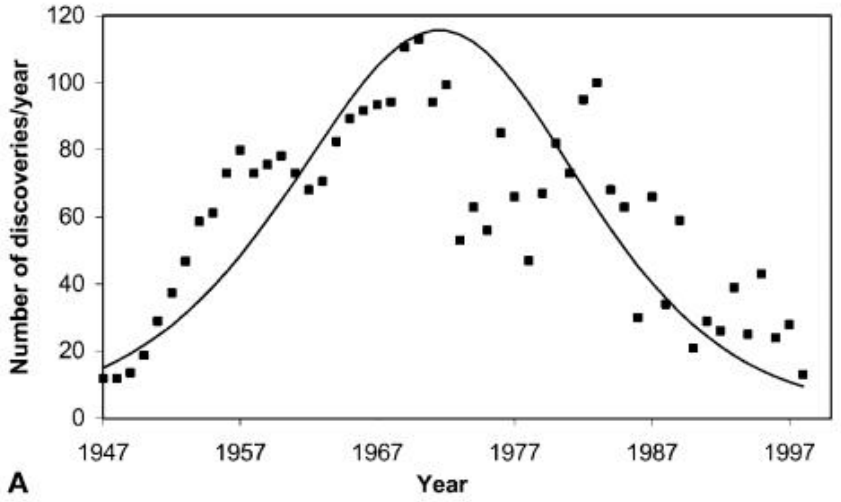

"…even if we accept the more conservative estimate, only about 3% of the existing compounds have been reported so far."

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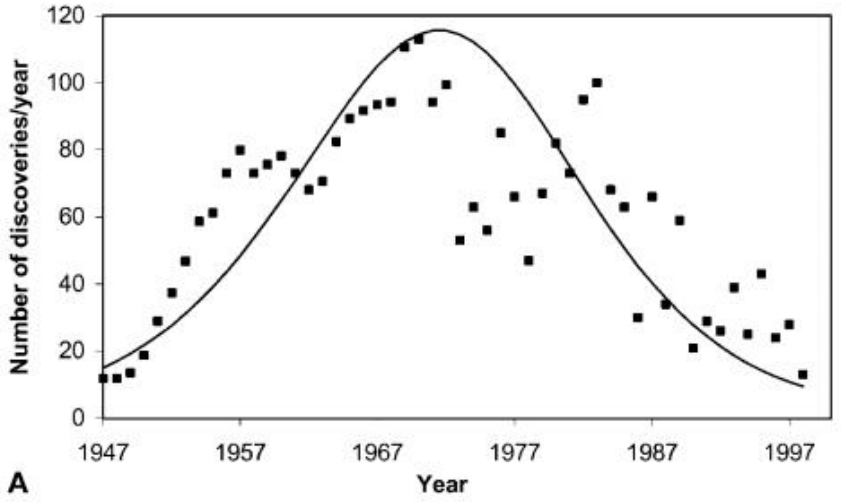

"…even if we accept the more conservative estimate, only about 3% of the existing compounds have been reported so far."

Problems:

1. **Rediscovery of commonly occurring compounds**
2. **Only tested in limited assays**

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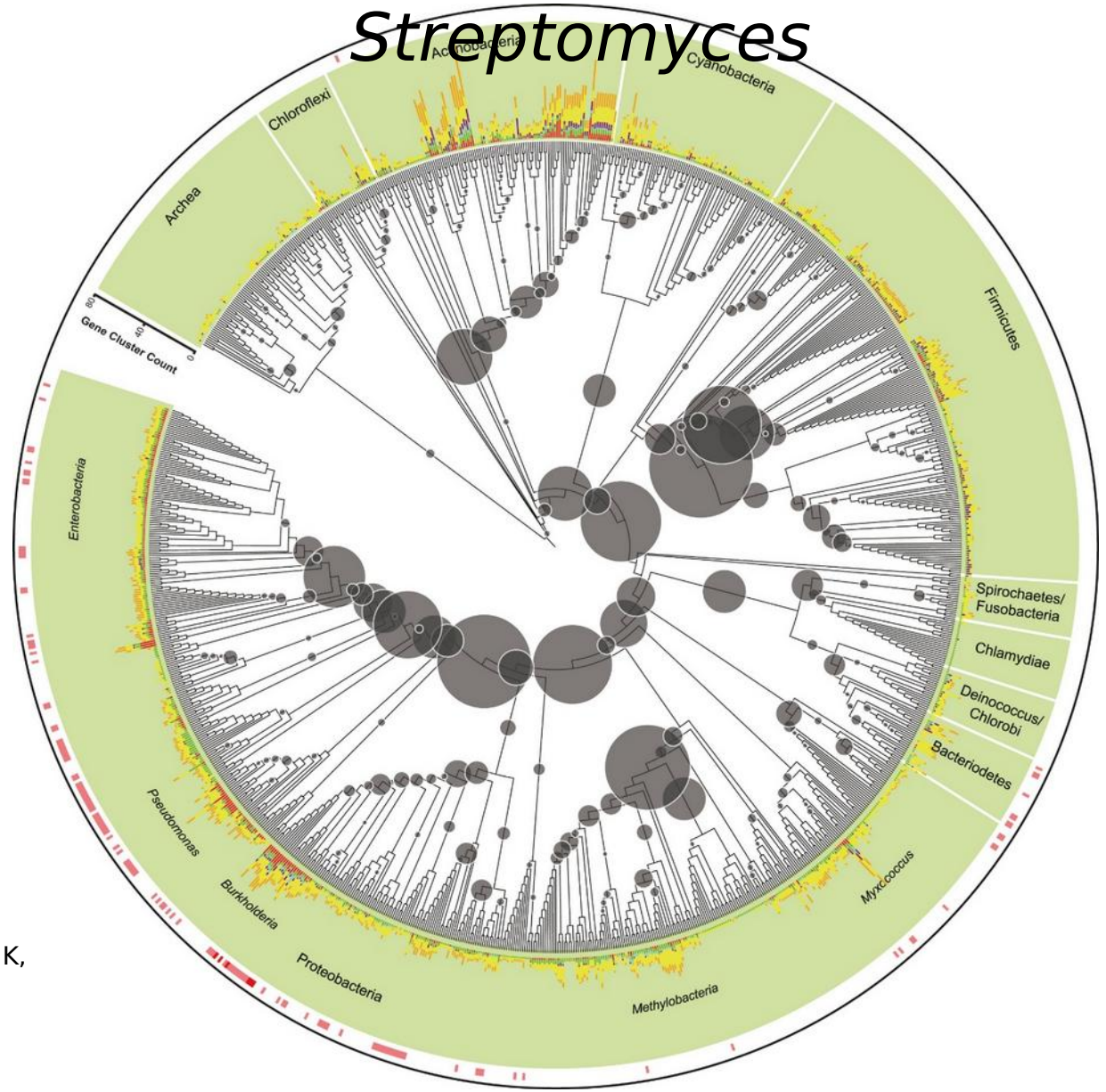
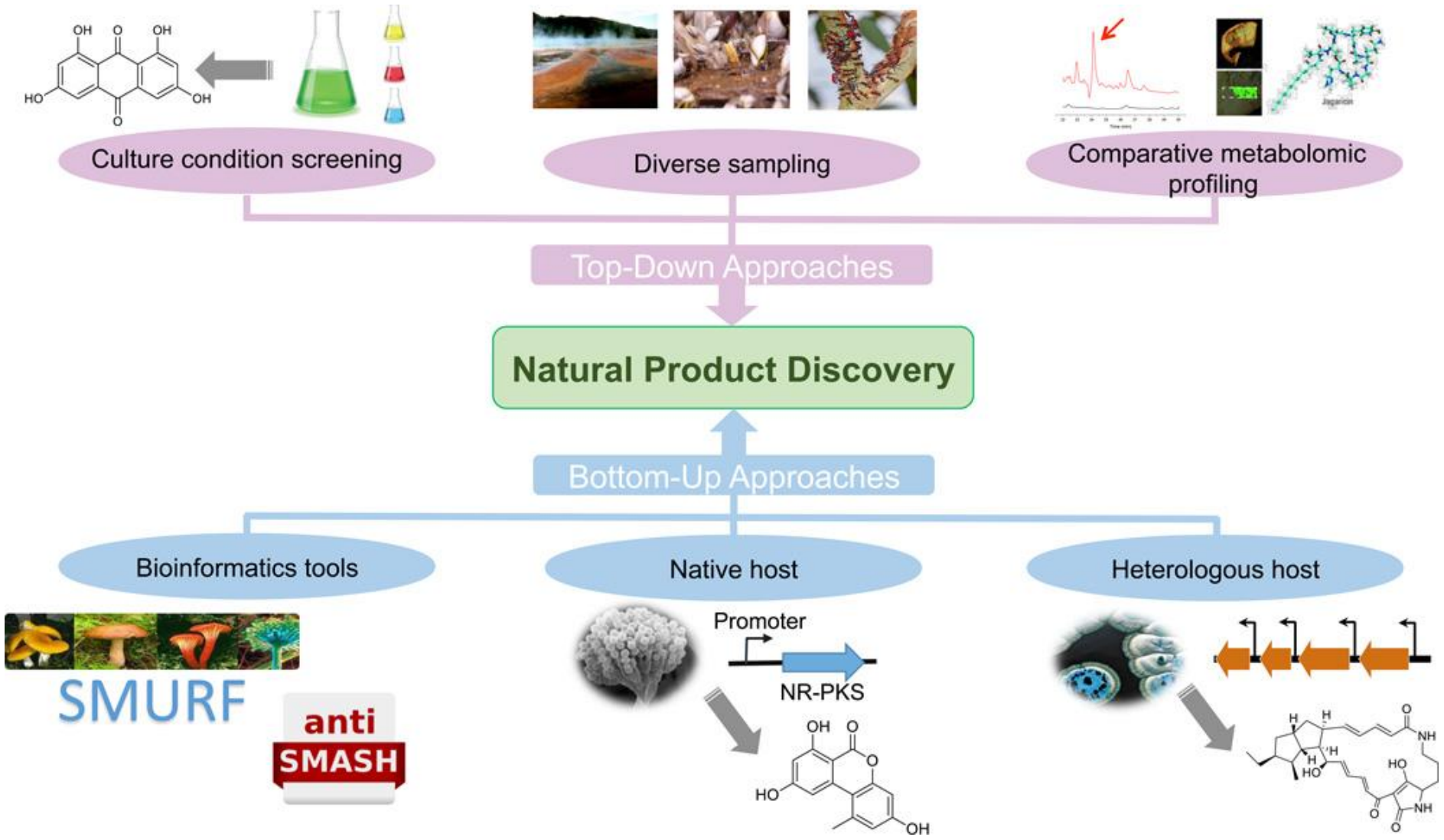
But… natural products aren’t just found in *Streptomyces*



Cimermancic P, Medema MH, Claesen J, Kurita K, Wieland Brown LC, Mavrommatis K, Pati A, Godfrey PA, Koehrsen M, Clardy J, Birren BW, Takano E, Sali A, Linington RG, Fischbach MA. Insights into secondary metabolism from a global analysis of prokaryotic biosynthetic gene clusters. Cell. Cell Press; 2014 Jul 17;158(2):412–421.

To think about…

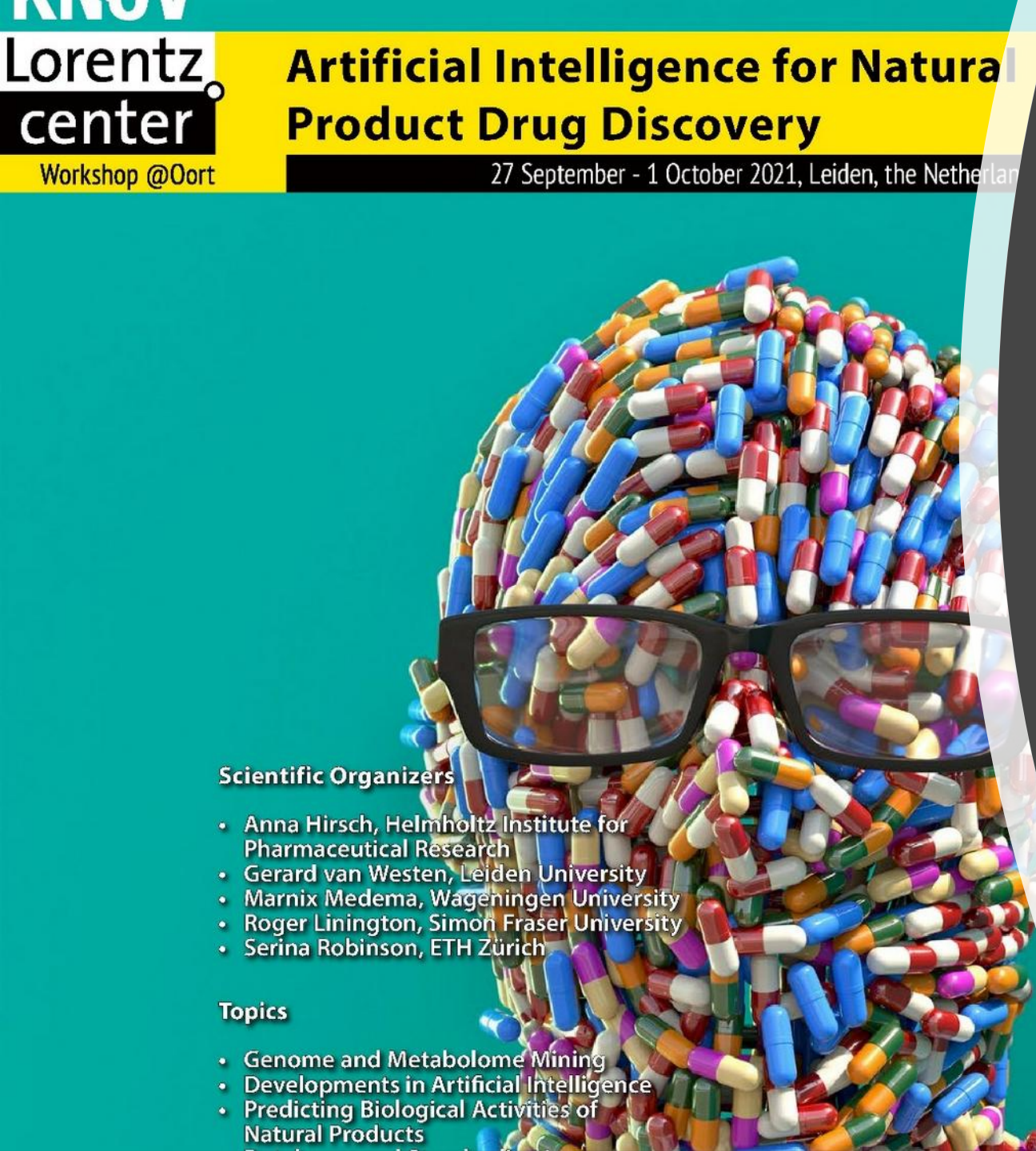
- Where should we look for new bacterial NP? (rediscovery of known compounds a major issue)
  - New species of bacteria? New phyla?
  - Same species, different location/host organism?
- How to access enough NP from uncultured organisms?
  - Total synthesis can be slow isn’t always an answer



Luo, Yunzi et al. “Recent advances in natural product discovery.” *Current opinion in biotechnology* vol. 30 (2014): 230-7. doi:10.1016/j.copbio.2014.09.002

Postdoctoral Research

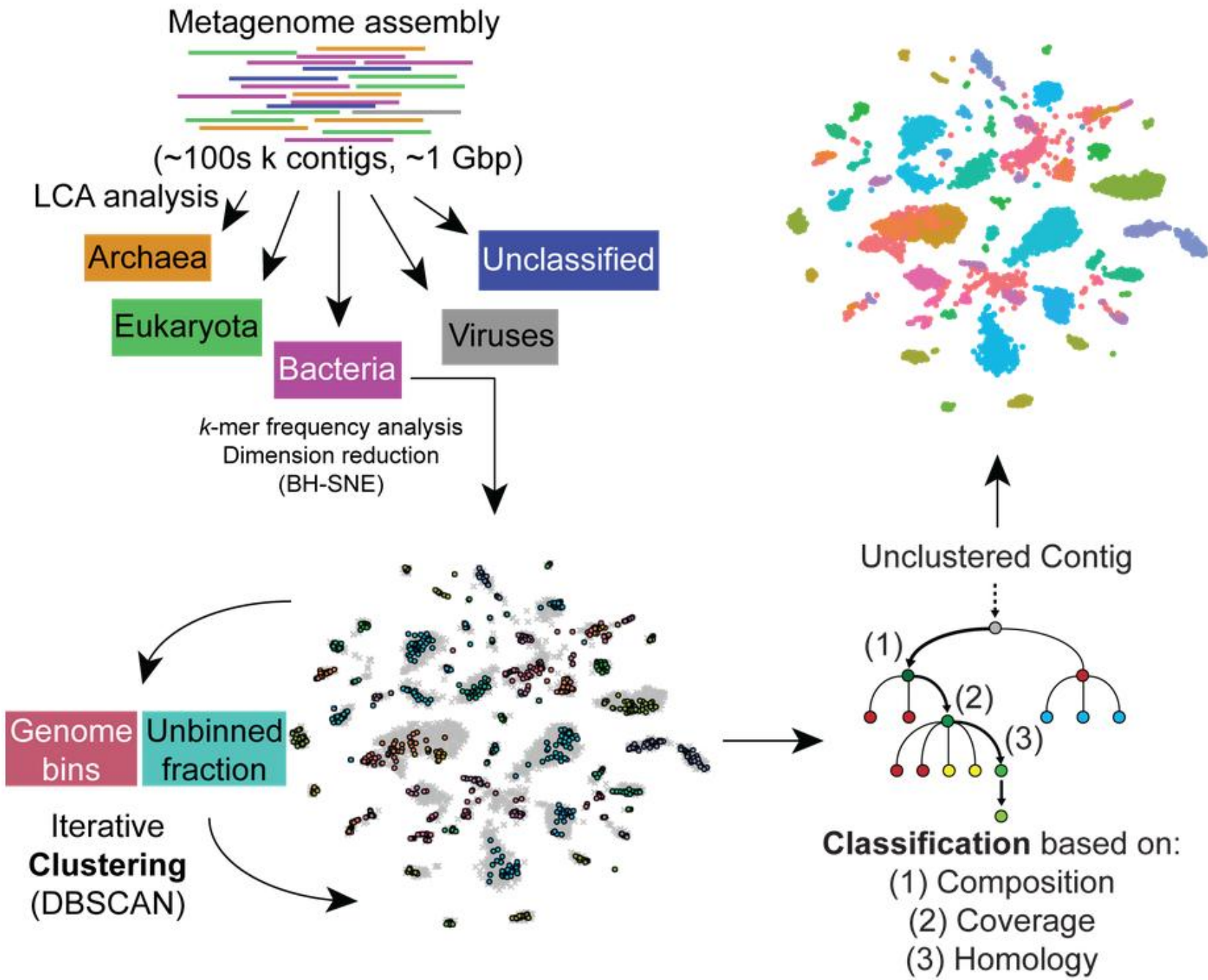
Bioinformatics, Metagenomics



Artificial Intelligence Approaches to Natural Product Drug Discovery

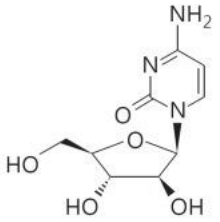
Nature Reviews Drug Discovery - submitted

(58 authors)



Miller IJ, et al. Autometa: automated extraction of microbial genomes from individual shotgun metagenomes. Nucleic Acids Res. 2019 Jun 4;47(10):e57.

“Natural Products”



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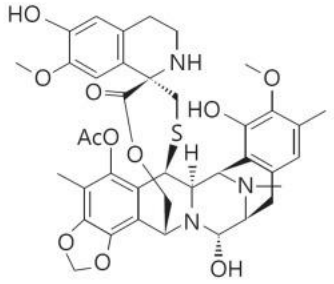

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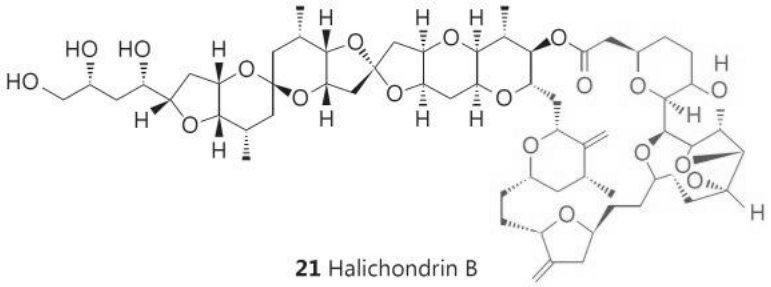

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PHOTO BY LAURA FLÓREZ

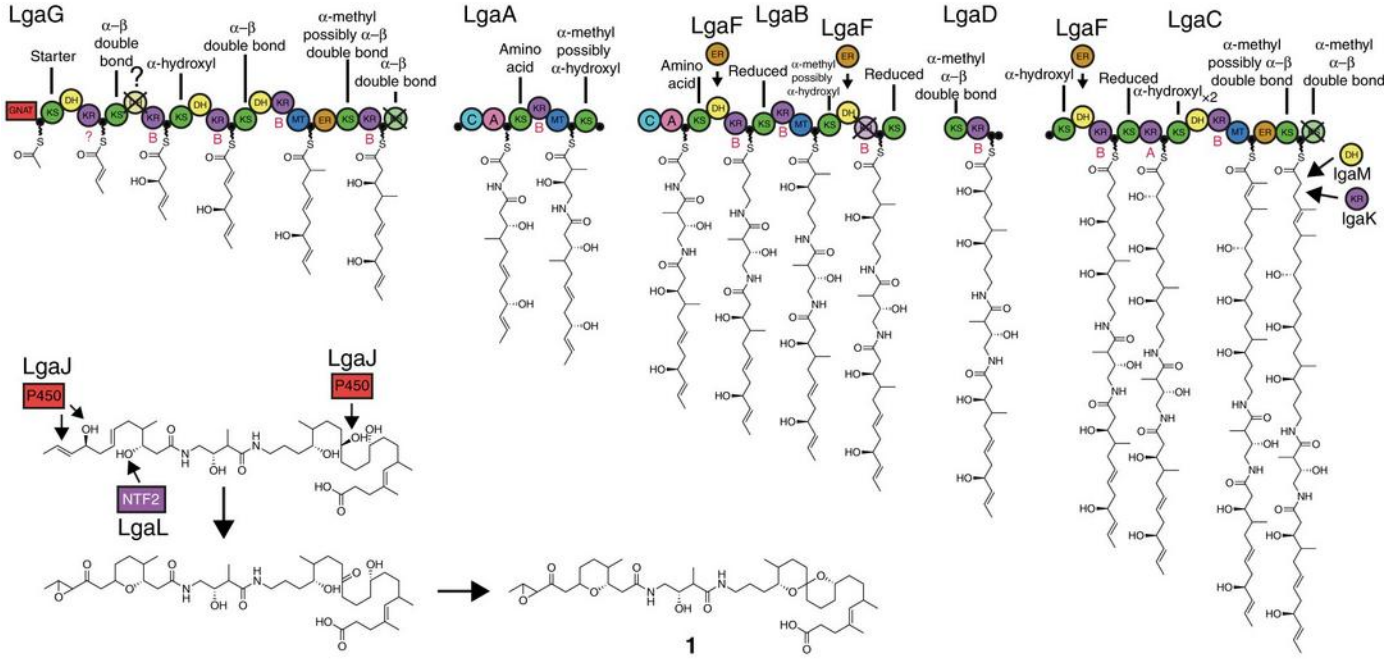
Metagenomic

Uncultured symbiont

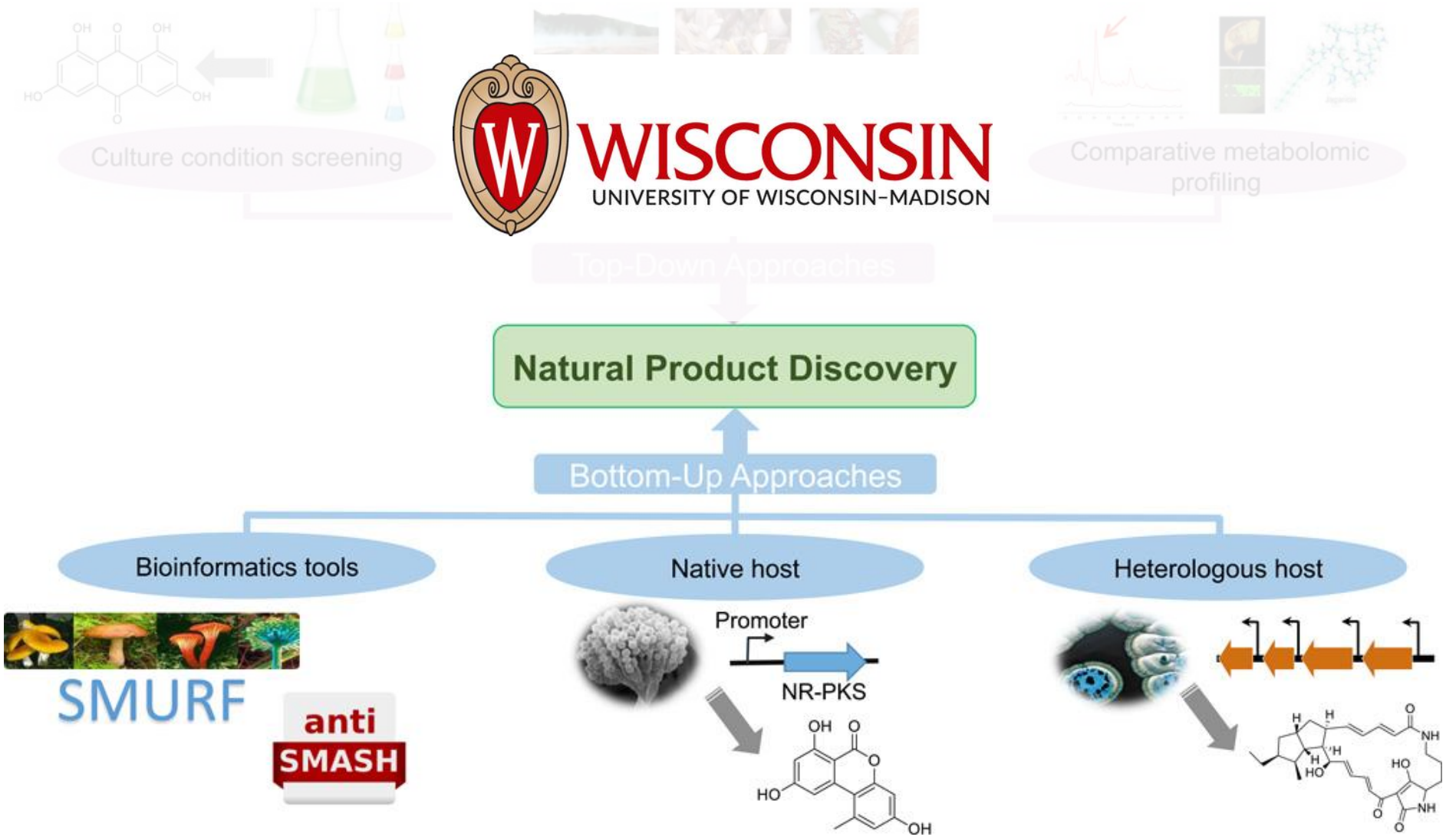
Burkholderia gladioli

Lv S+R

Metagenomics revealed the biosynthetic gene cluster for lagriamide



Waterworth SC, Flórez LV, Rees ER, Hertweck C, Kaltenpoth M, Kwan JC. Horizontal Gene Transfer to a Defensive Symbiont with a Reduced Genome in a Multipartite Beetle Microbiome. mBio. 2020 Feb 25;11(1):e02430-19.



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SocialGene

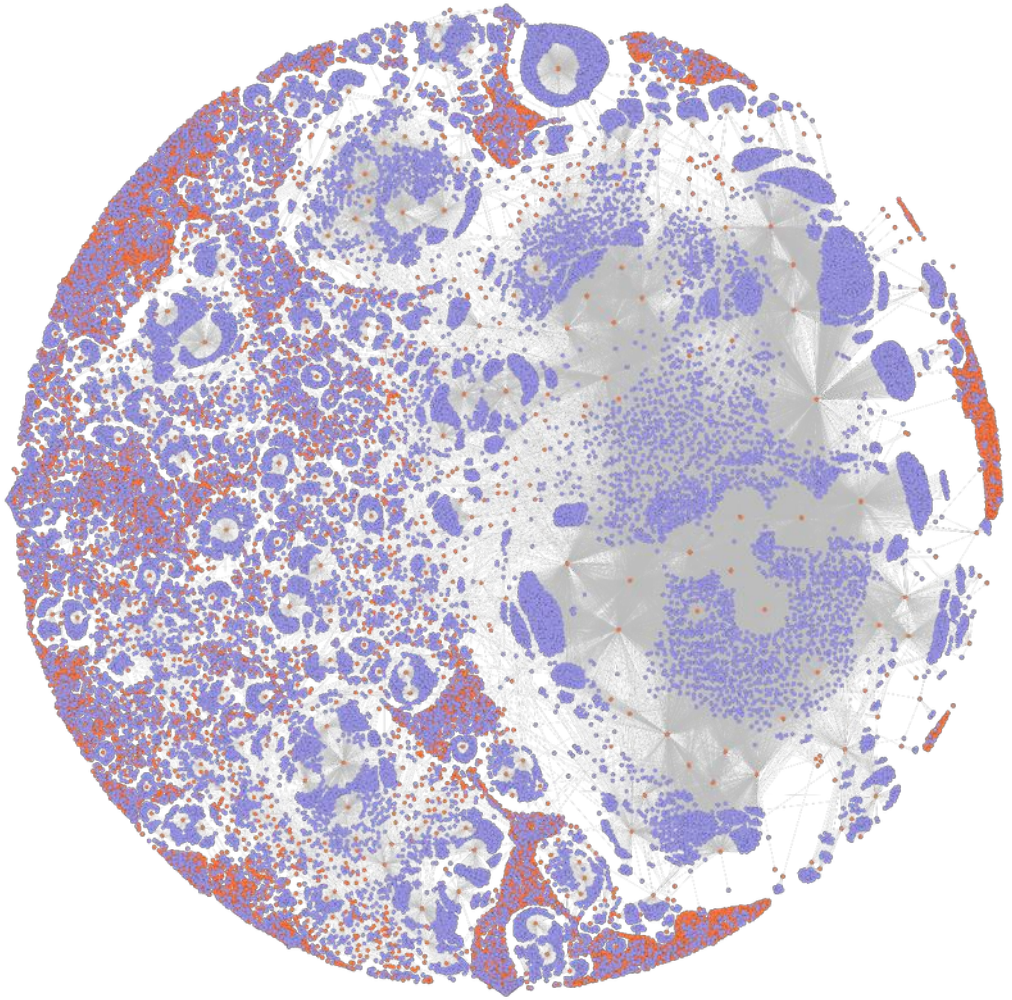
Knowledge graphs for drug discovery
Functional characterization of proteins
and searching for similar BGCs

python™

nextflow

django

neo4j



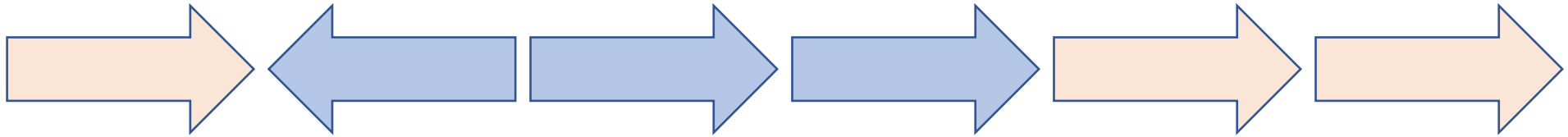
Molecular Biology in < 1 minute

DNA -> RNA, RNA -> protein

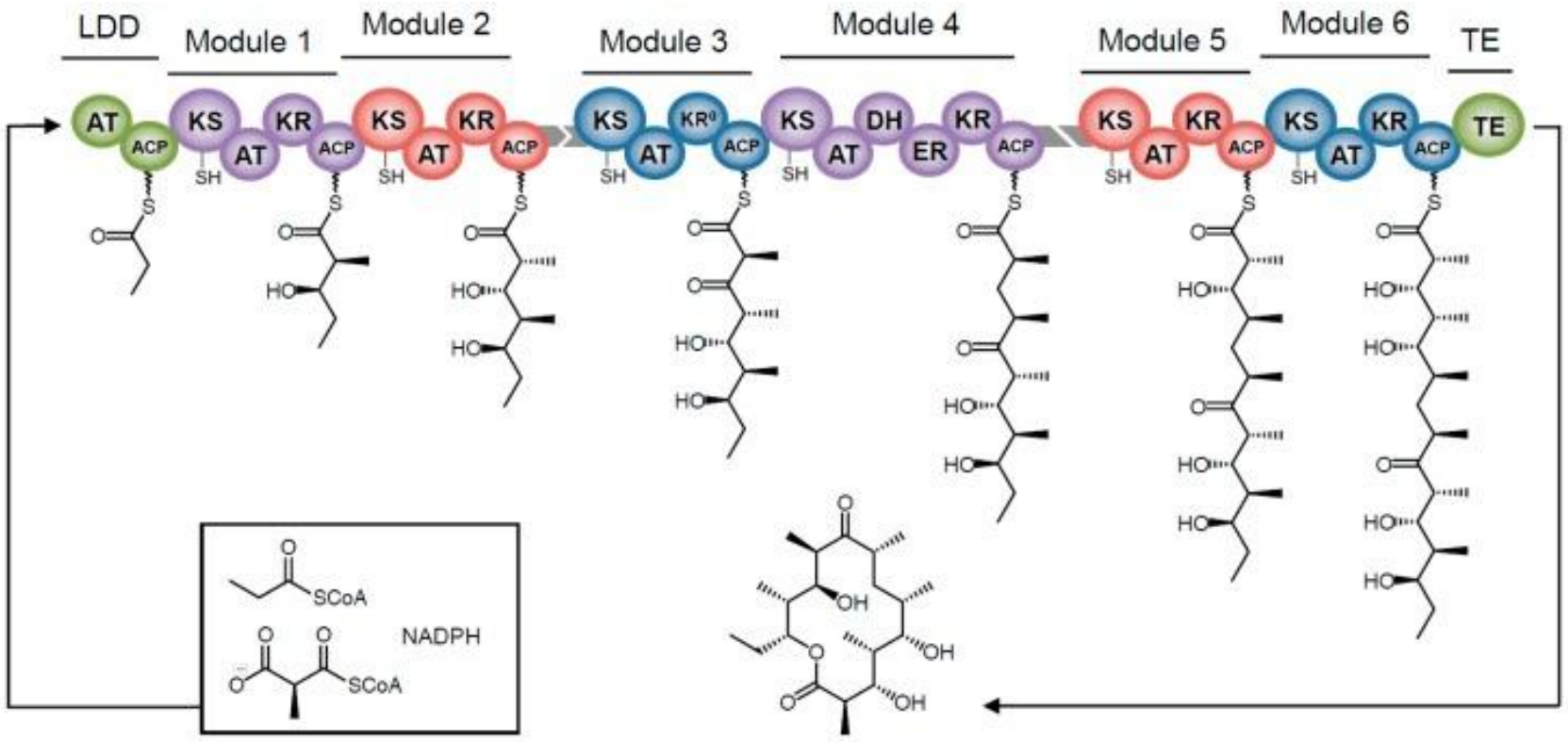
DNA (nucleotides)	ATGTCCAACGCC...	CGCGGCATCCTC...	GGCGCCGTGCTC...
RNA (nucleotides)	UTG|TCC|UUC|GCC|...	CGC|GGC|UTC|CTC|...	GGC|GCC|GTG|CTC|...
Proteins (amino acids)	MSNARATHLTRRGI...	KADVQAGDMDVSK...	AKSGPWTFKDDRGT...
Protein have domains	MSNARATHLTRRGI...	KADVQAGDMDVSK...	AKSGPWTFKDDRGT...

Genes encode proteins

Gene Cluster



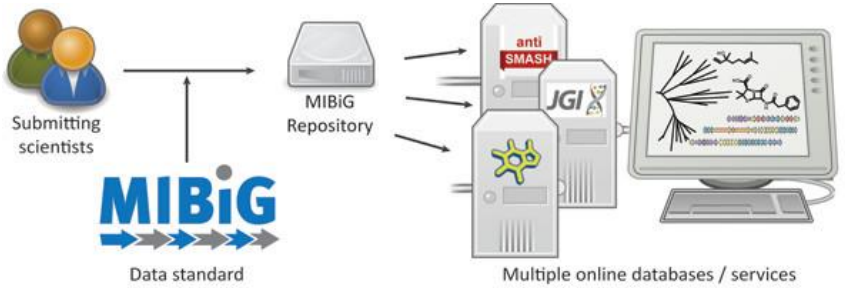
Polyketide synthases are large, multidomain proteins “Beads on a String”



Bayly, Carmen L, and Vikramaditya G Yadav. “Towards Precision Engineering of Canonical Polyketide Synthase Domains: Recent Advances and Future Prospects.” *Molecules (Basel, Switzerland)*vol. 22,2 235. 5 Feb. 2017, doi:10.3390/molecules22020235

Vignette 1

Mapping MIBiG



SocialGene

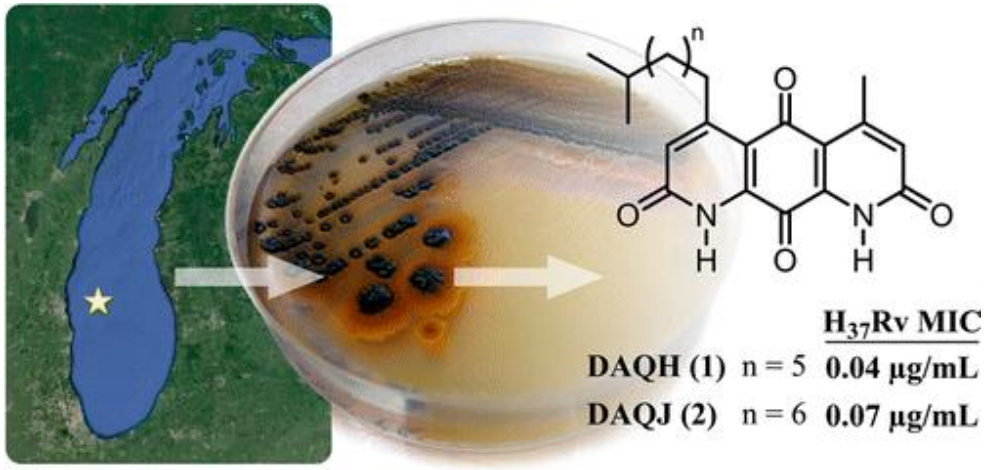
Non-redundant protein

HMM model

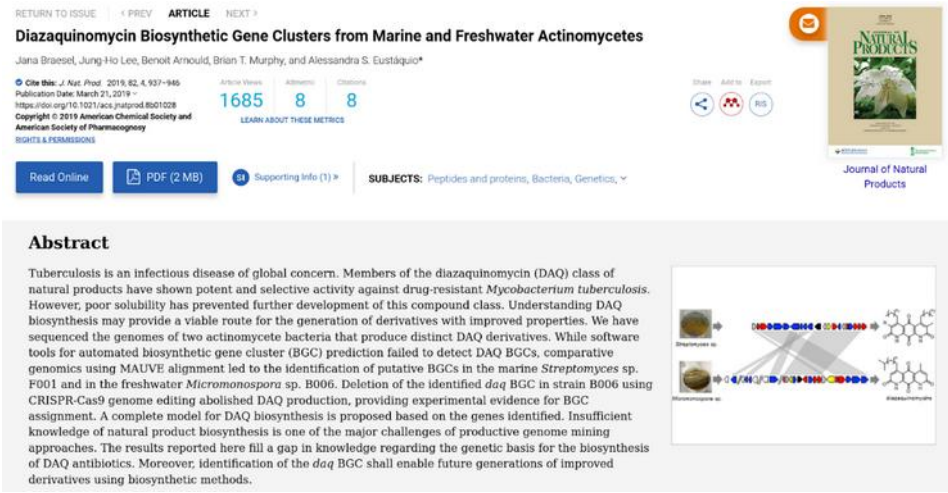
prenyltransferases
terpene synthases
DAHP synthases
geranylgeranyl pyrophosphate synthases
AraC family transcriptional regulators
aspartokinases
pentacyclic cyclases
nucleotidyltransferases
aldehyde dehydrogenases
glutathione-S-transferases
ectoine synathases
acetyltransferases
glyoxalase/bleomycin resistance proteins
acyl CoA dehydrogenases
PKS cyclases
dioxygenases
ferredoxin reductases
aminotransferases
halogenases
monooxygenases
PKS cyclases
metallo-beta-lactamases
n-acetyltransferases
asparagine synthases
TetR (transcriptional regulator)
HMG-CoA ERssynthases
4'-PPTases
ACPs
transcriptional regulators
glycosyltransferases
dehydrogenases
dehydratases
reductases
transposases
prism glycosyltransferase
PKS
P450s
antismash- SMCOG1041 SARP_family
Methyltransferases
SAM dependent methyltransferases
PKS/NRPS
Esterases
carboxyl transferases
aminotransferases
Thioesterases
cycloisomerases
transcriptional regulators
NRPS
transcriptional regulators
hexose epimerases
amide-ligases
transcriptional regulators
transposases
luciferase-like monooxygenases
hexose 2,3 dehydrateses
two-component system histidine kinases sensor histidine kinases
amidohydolases
DoxX family transporters
peptidases
SMR-type multi-drug efflux transporters
transcriptional regulators
prenyltransferases
LysE family transporters
antibiotic transporters
transketolases
2-oxoglutarate ferredoxin oxidoreductase beta subunit
"membrane proteins"
penicillin binding proteins
mix of specific transporters
transcription factors
major facilitator superfamily (membrane transporters)
anthranilate synthases
ABC transporters

Vignette 2

Looking for diazaquinomycin analogs



Mullowney, Michael W et al. “Diaza-anthracene Antibiotics from a Freshwater-Derived Actinomycete with Selective Antibacterial Activity toward *Mycobacterium tuberculosis*.” *ACS infectious diseases* vol. 1,4 (2015): 168-174. doi:10.1021/acsinfecdis.5b00005



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Diazaquinomycin Biosynthetic Gene Clusters from Marine and Freshwater Actinomycetes

Jana Braesel, Jung-Ho Lee, Benoit Arnould, Brian T. Murphy, and Alessandra S. Eustáquio*

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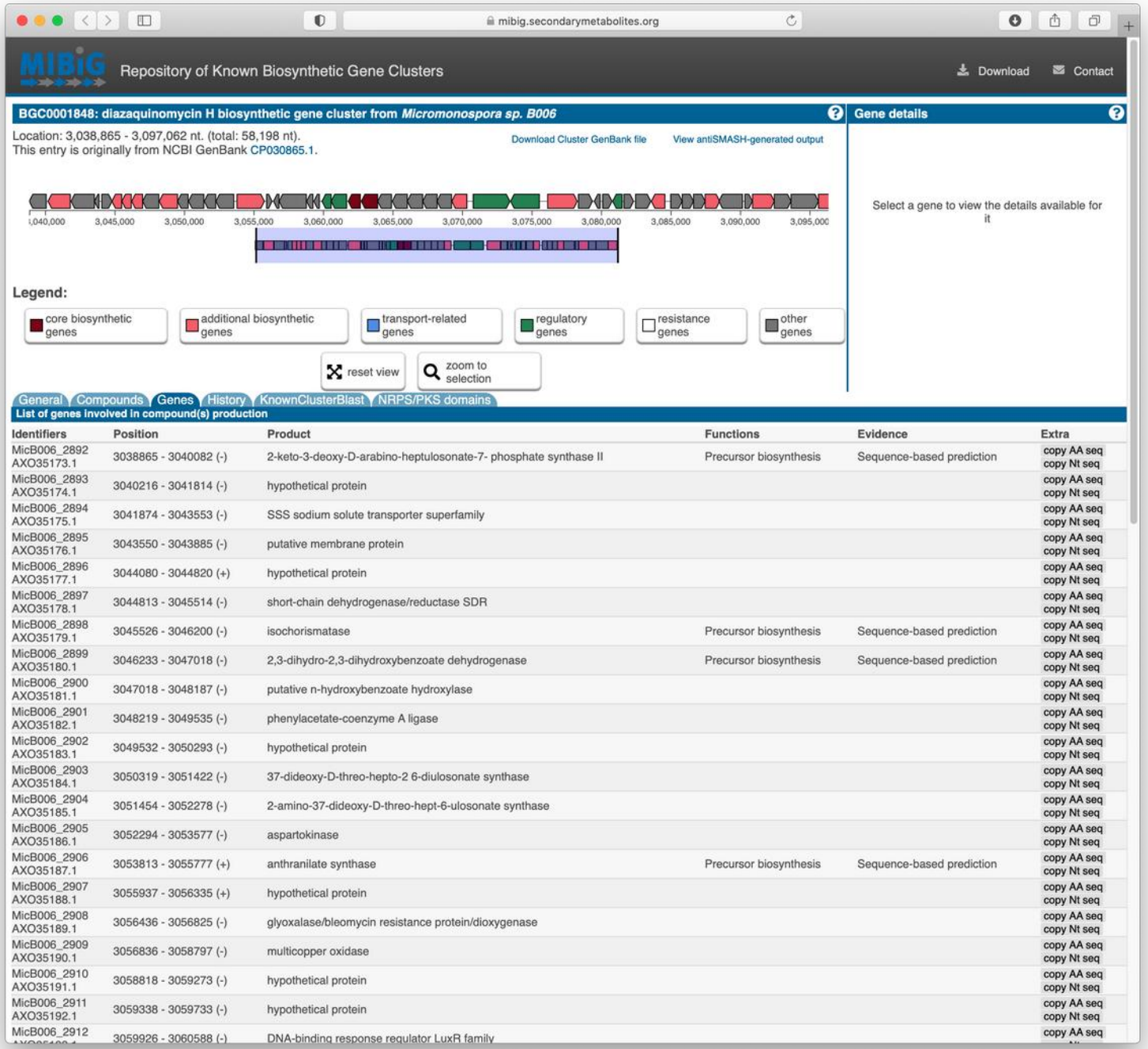
Journal of Natural Products

Abstract

Tuberculosis is an infectious disease of global concern. Members of the diazaquinomycin (DAQ) class of natural products have shown potent and selective activity against drug-resistant *Mycobacterium tuberculosis*. However, poor solubility has prevented further development of this compound class. Understanding DAQ biosynthesis may provide a viable route for the generation of derivatives with improved properties. We have sequenced the genomes of two actinomycete bacteria that produce distinct DAQ derivatives. While software tools for automated biosynthetic gene cluster (BGC) prediction failed to detect DAQ BGCs, comparative genomics using MAUVE alignment led to the identification of putative BGCs in the marine *Streptomyces* sp. F001 and in the freshwater *Micromonospora* sp. B006. Deletion of the identified *daq* BGC in strain B006 using CRISPR-Cas9 genome editing abolished DAQ production, providing experimental evidence for BGC assignment. A complete model for DAQ biosynthesis is proposed based on the genes identified. Insufficient knowledge of natural product biosynthesis is one of the major challenges of productive genome mining approaches. The results reported here fill a gap in knowledge regarding the genetic basis for the biosynthesis of DAQ antibiotics. Moreover, identification of the *daq* BGC shall enable future generations of improved derivatives using biosynthetic methods.



mibig.secondarymetabolites.org

MIBiG Repository of Known Biosynthetic Gene Clusters

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BGC0001848: diazaquinomycin H biosynthetic gene cluster from *Micromonospora sp. B006*

Location: 3,038,865 - 3,097,062 nt. (total: 58,198 nt).
This entry is originally from NCBI GenBank CP030865.1.

Download Cluster GenBank file | View antiSMASH-generated output

,040,000 3,045,000 3,050,000 3,055,000 3,060,000 3,065,000 3,070,000 3,075,000 3,080,000 3,085,000 3,090,000 3,095,000

Legend:

core biosynthetic genes | additional biosynthetic genes | transport-related genes | regulatory genes | resistance genes | other genes

reset view | zoom to selection

Gene details

Select a gene to view the details available for it

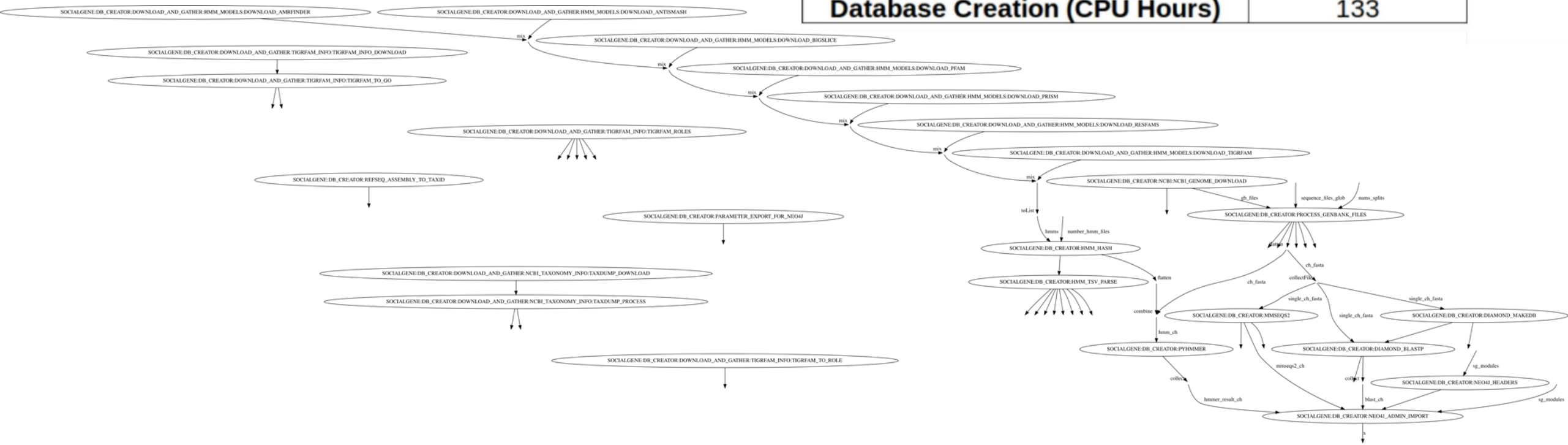
General | Compounds | Genes | History | KnownClusterBlast | NRPS/PKS domains

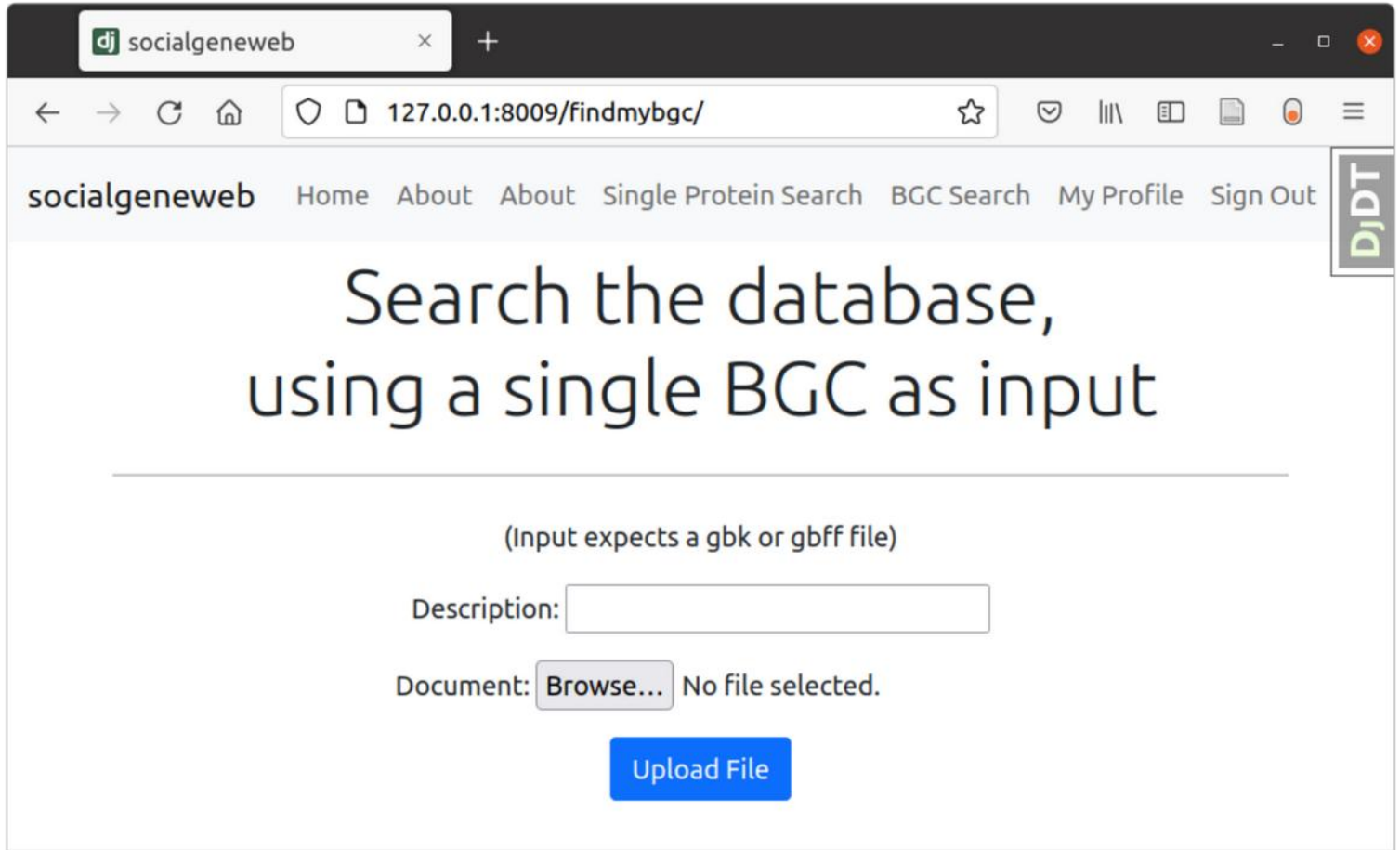
List of genes involved in compound(s) production

Identifiers	Position	Product	Functions	Evidence	Extra
MicB006_2892 AXO35173.1	3038865 - 3040082 (-)	2-keto-3-deoxy-D-arabino-heptulosonate-7- phosphate synthase II	Precursor biosynthesis	Sequence-based prediction	copy AA seq copy Nt seq
MicB006_2893 AXO35174.1	3040216 - 3041814 (-)	hypothetical protein			copy AA seq copy Nt seq
MicB006_2894 AXO35175.1	3041874 - 3043553 (-)	SSS sodium solute transporter superfamily			copy AA seq copy Nt seq
MicB006_2895 AXO35176.1	3043550 - 3043885 (-)	putative membrane protein			copy AA seq copy Nt seq
MicB006_2896 AXO35177.1	3044080 - 3044820 (+)	hypothetical protein			copy AA seq copy Nt seq
MicB006_2897 AXO35178.1	3044813 - 3045514 (-)	short-chain dehydrogenase/reductase SDR			copy AA seq copy Nt seq
MicB006_2898 AXO35179.1	3045526 - 3046200 (-)	isochorismatase	Precursor biosynthesis	Sequence-based prediction	copy AA seq copy Nt seq
MicB006_2899 AXO35180.1	3046233 - 3047018 (-)	2,3-dihydro-2,3-dihydroxybenzoate dehydrogenase	Precursor biosynthesis	Sequence-based prediction	copy AA seq copy Nt seq
MicB006_2900 AXO35181.1	3047018 - 3048187 (-)	putative n-hydroxybenzoate hydroxylase			copy AA seq copy Nt seq
MicB006_2901 AXO35182.1	3048219 - 3049535 (-)	phenylacetate-coenzyme A ligase			copy AA seq copy Nt seq
MicB006_2902 AXO35183.1	3049532 - 3050293 (-)	hypothetical protein			copy AA seq copy Nt seq
MicB006_2903 AXO35184.1	3050319 - 3051422 (-)	37-dideoxy-D-threo-hepto-2 6-diulosonate synthase			copy AA seq copy Nt seq
MicB006_2904 AXO35185.1	3051454 - 3052278 (-)	2-amino-37-dideoxy-D-threo-hept-6-ulosonate synthase			copy AA seq copy Nt seq
MicB006_2905 AXO35186.1	3052294 - 3053577 (-)	aspartokinase			copy AA seq copy Nt seq
MicB006_2906 AXO35187.1	3053813 - 3055777 (+)	anthranilate synthase	Precursor biosynthesis	Sequence-based prediction	copy AA seq copy Nt seq
MicB006_2907 AXO35188.1	3055937 - 3056335 (+)	hypothetical protein			copy AA seq copy Nt seq
MicB006_2908 AXO35189.1	3056436 - 3056825 (-)	glyoxalase/bleomycin resistance protein/dioxygenase			copy AA seq copy Nt seq
MicB006_2909 AXO35190.1	3056836 - 3058797 (-)	multicopper oxidase			copy AA seq copy Nt seq
MicB006_2910 AXO35191.1	3058818 - 3059273 (-)	hypothetical protein			copy AA seq copy Nt seq
MicB006_2911 AXO35192.1	3059338 - 3059733 (-)	hypothetical protein			copy AA seq copy Nt seq
MicB006_2912	3059926 - 3060588 (-)	DNA-binding response regulator LuxR family			copy AA seq

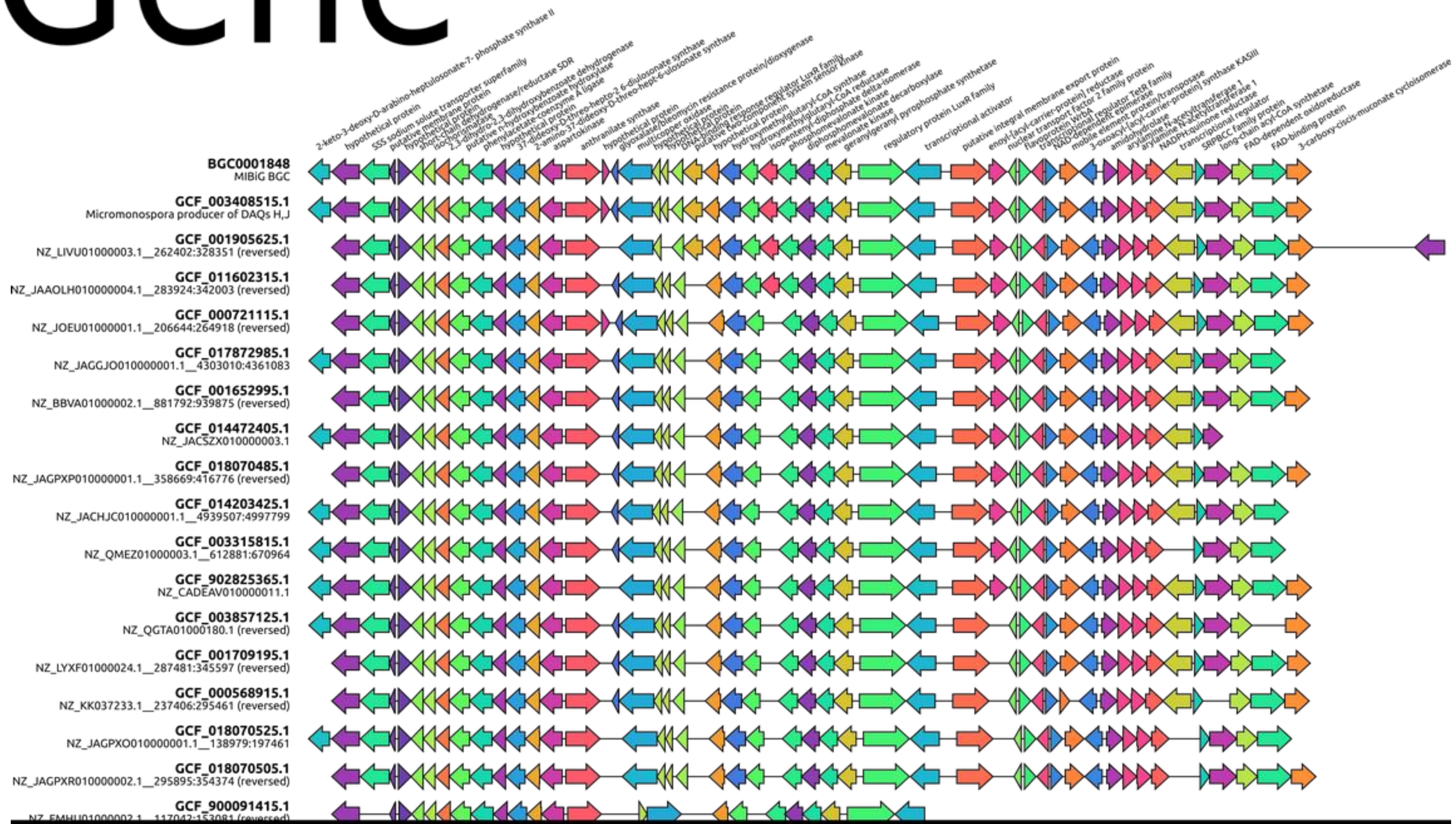
SocialGene

	Micromonospora
Genomes	226
Contigs/Scaffolds	34,856
Proteins	1,373,641
Non-Redundant Proteins	1,076,690
HMM Annotations	10,656,754
MMSEQS2	1,009,056
Bidirectional BLASTP (45.3 GB)	420,788,981
Database Creation (Real Duration)	4h 30m
Database Creation (CPU Hours)	133




socialgeneweb
127.0.0.1:8009/findmybgc/
socialgeneweb
Home
About
About
Single Protein Search
BGC Search
My Profile
Sign Out
DjDT
Search the database,
using a single BGC as input
(Input expects a gbk or gbff file)
Description:
Document:
Browse...
No file selected.
Upload File

SocialGene


BGC0001848
MIBiG BGC
GCF_003408515.1
Micromonospora producer of DAQs H,J
GCF_001905625.1
NZ_LIVU01000003.1__262402:328351 (reversed)
GCF_011602315.1
NZ_JAAOLH010000004.1__283924:342003 (reversed)
GCF_000721115.1
NZ_JOEU01000001.1__206644:264918 (reversed)
GCF_017872985.1
NZ_JAGGJO010000001.1__4303010:4361083
GCF_001652995.1
NZ_BBVA01000002.1__881792:939875 (reversed)
GCF_014472405.1
NZ_JACSZX010000003.1
GCF_018070485.1
NZ_JAGPXP010000001.1__358669:416776 (reversed)
GCF_014203425.1
NZ_JACHJC010000001.1__4939507:4997799
GCF_003315815.1
NZ_QMEZ01000003.1__612881:670964
GCF_902825365.1
NZ_CADEAV010000011.1
GCF_003857125.1
NZ_QGTA01000180.1 (reversed)
GCF_001709195.1
NZ_LYXF01000024.1__287481:345597 (reversed)
GCF_000568915.1
NZ_KK037233.1__237406:295461 (reversed)
GCF_018070525.1
NZ_JAGPXO010000001.1__138979:197461
GCF_018070505.1
NZ_JAGPXR010000002.1__295895:354374 (reversed)
GCF_900091415.1

	Micromonospora
Genomes	226
Contigs/Scaffolds	34,856
Proteins	1,373,641
Non-Redundant Proteins	1,076,690
HMM Annotations	10,656,754
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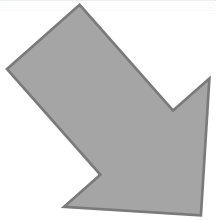
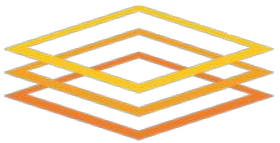
Database Creation (CPU Hours)	133

SocialGene

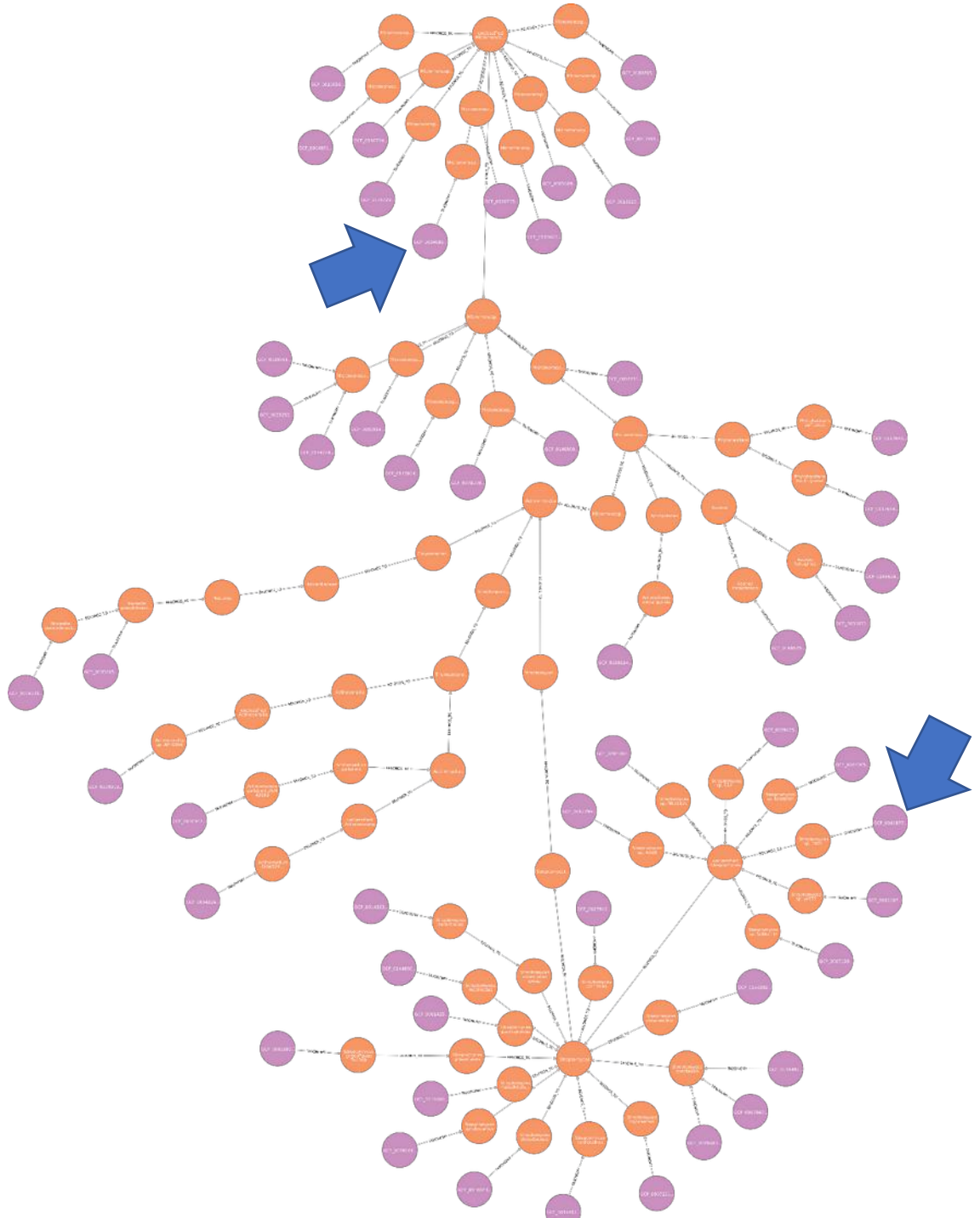


	RefSeq
Genomes	266,668
Contigs/Scaffolds	23,941,594
Proteins	188,429,555
HMM models	25,648
HMM annotations	1,403,423,051
MMseqs2 (bug in MMseqs2)	188,327,165
Contigs to Proteins	971,298,319
Species	49,902
Genera	6,460



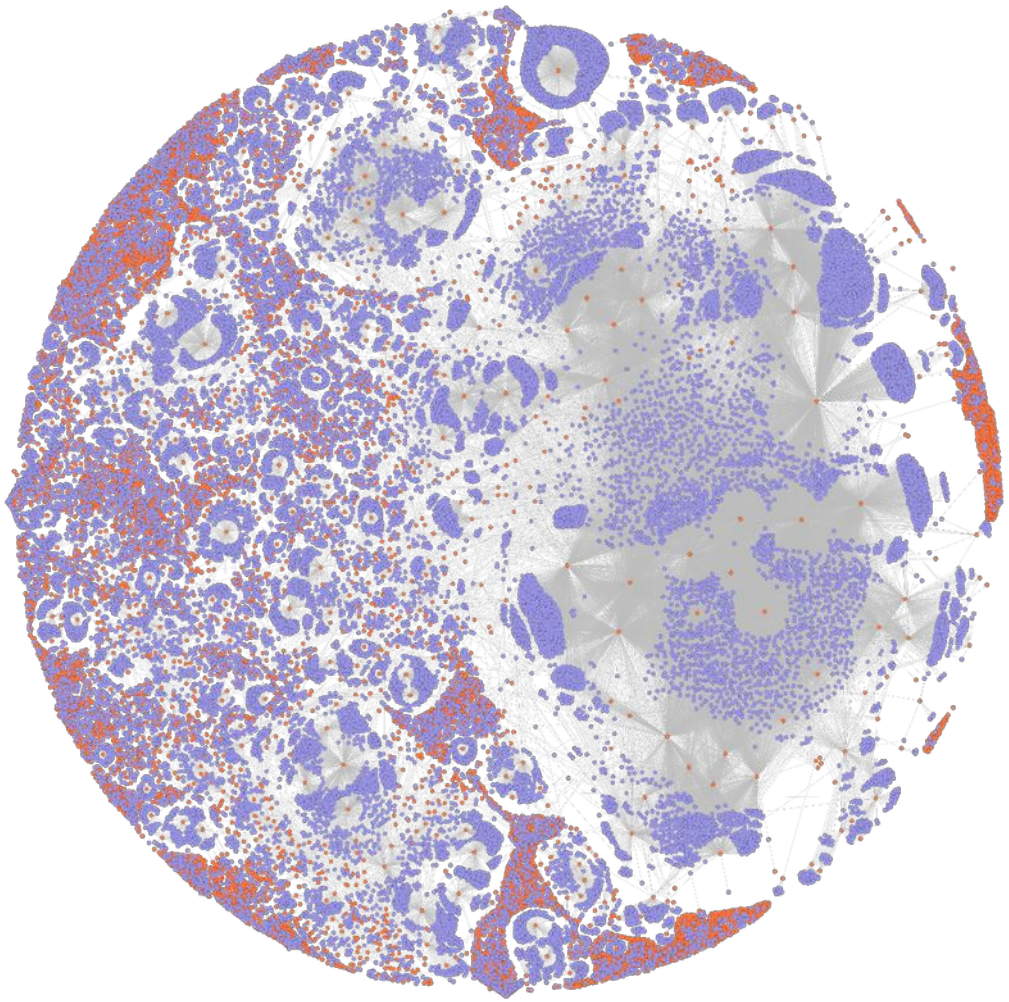
Open Science Grid

CENTER FOR HIGH THROUGHPUT COMPUTING



Teasers- What Next?

SocialGene

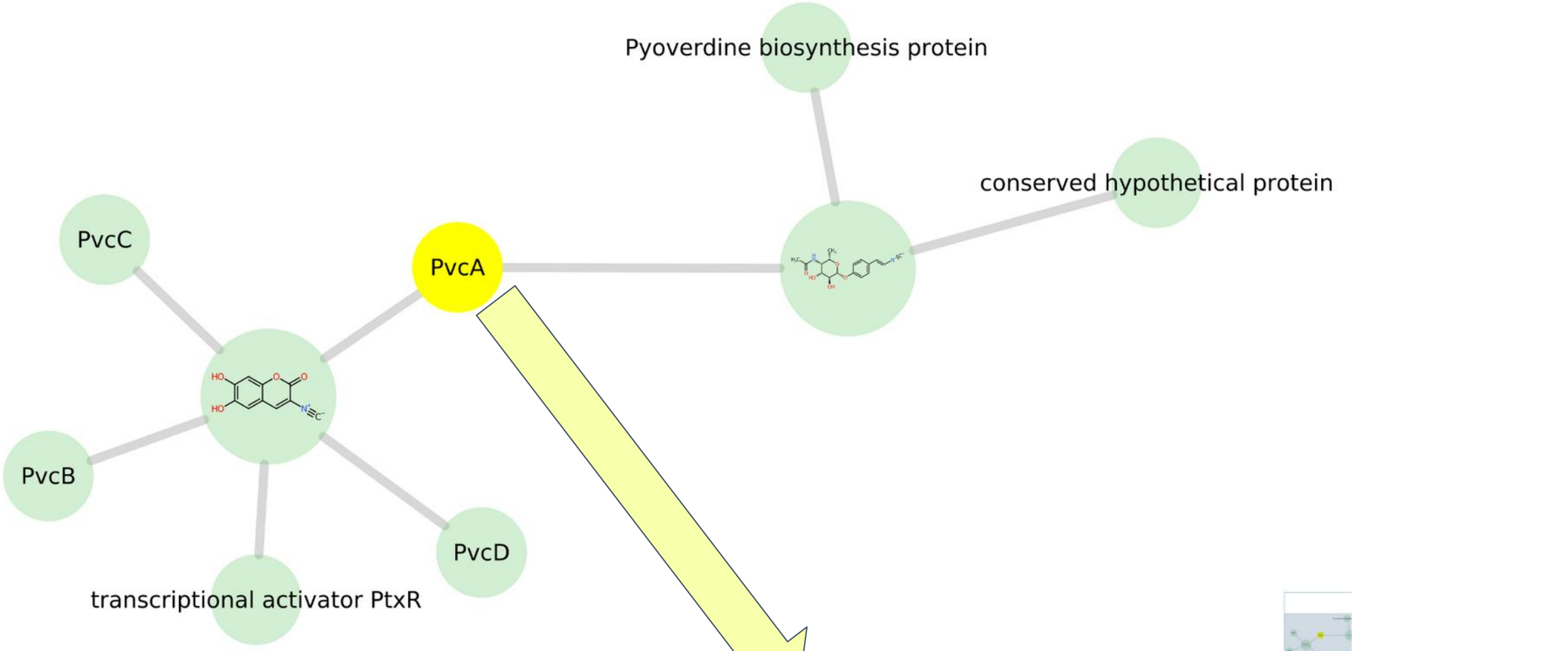


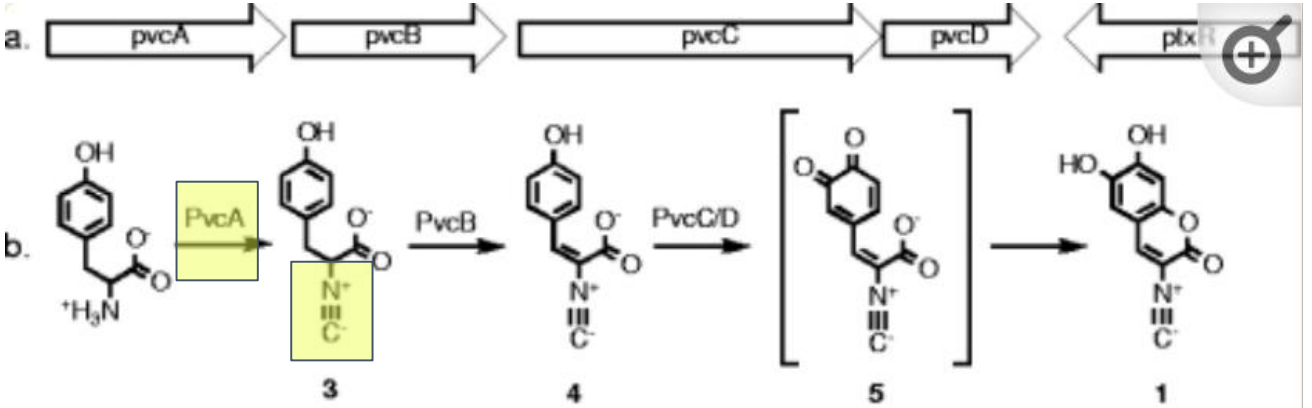
python™

nextflow

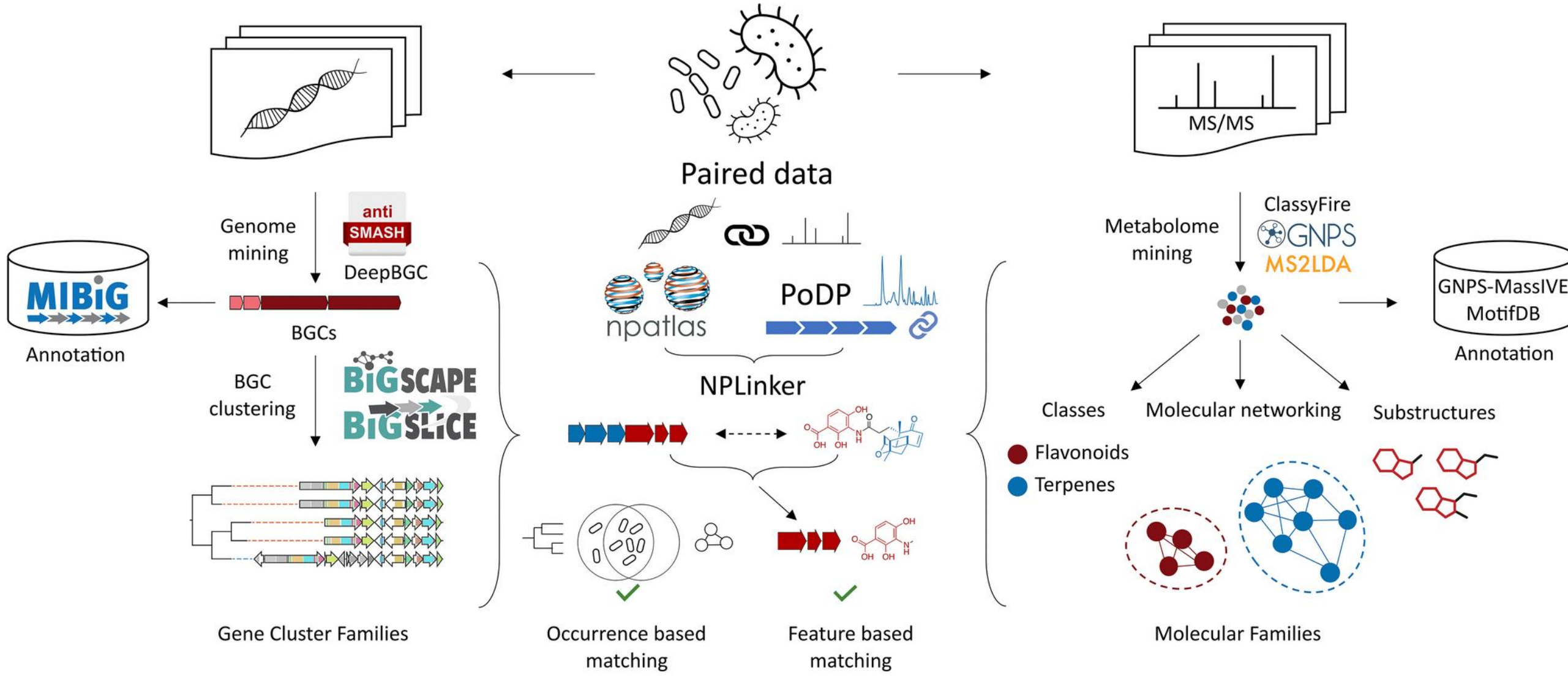
django

neo4j





Clarke-Pearson MF, Brady SF. Paerucumarin, a new metabolite produced by the pvc gene cluster from Pseudomonas aeruginosa. J Bacteriol. 2008 Oct;190(20):6927-30.



Louwen JJR, van der Hooft JJJ. Comprehensive Large-Scale Integrative Analysis of Omics Data To Accelerate Specialized Metabolite Discovery. mSystems. 2021 Aug 31;6(4):e0072621. doi: 10.1128/mSystems.00726-21. Epub 2021 Aug 24