Creating and leveraging bespoke large-scale knowledge graphs for comparative genomics and multi-omics drug discovery with SocialGene

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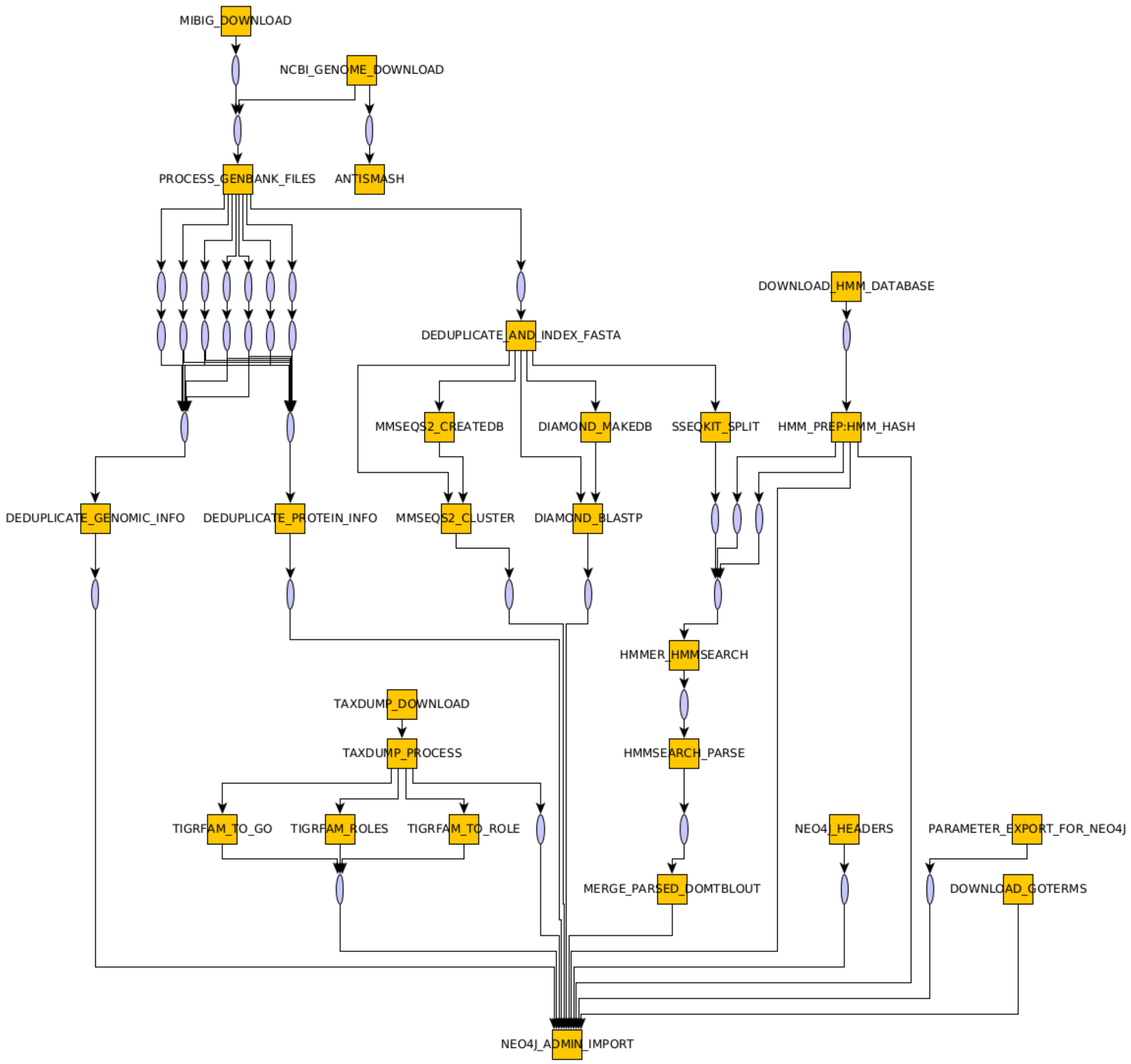
Supplementary Figure 1: Simplified outline of data processing



This outline shows a simplified outline of the automated steps taken by SocialGene's Python and Nextflow libraries to take input genomes and transform them into a Neo4j database. Square boxes represent an action or actions and ovals represent a file/unit of data.

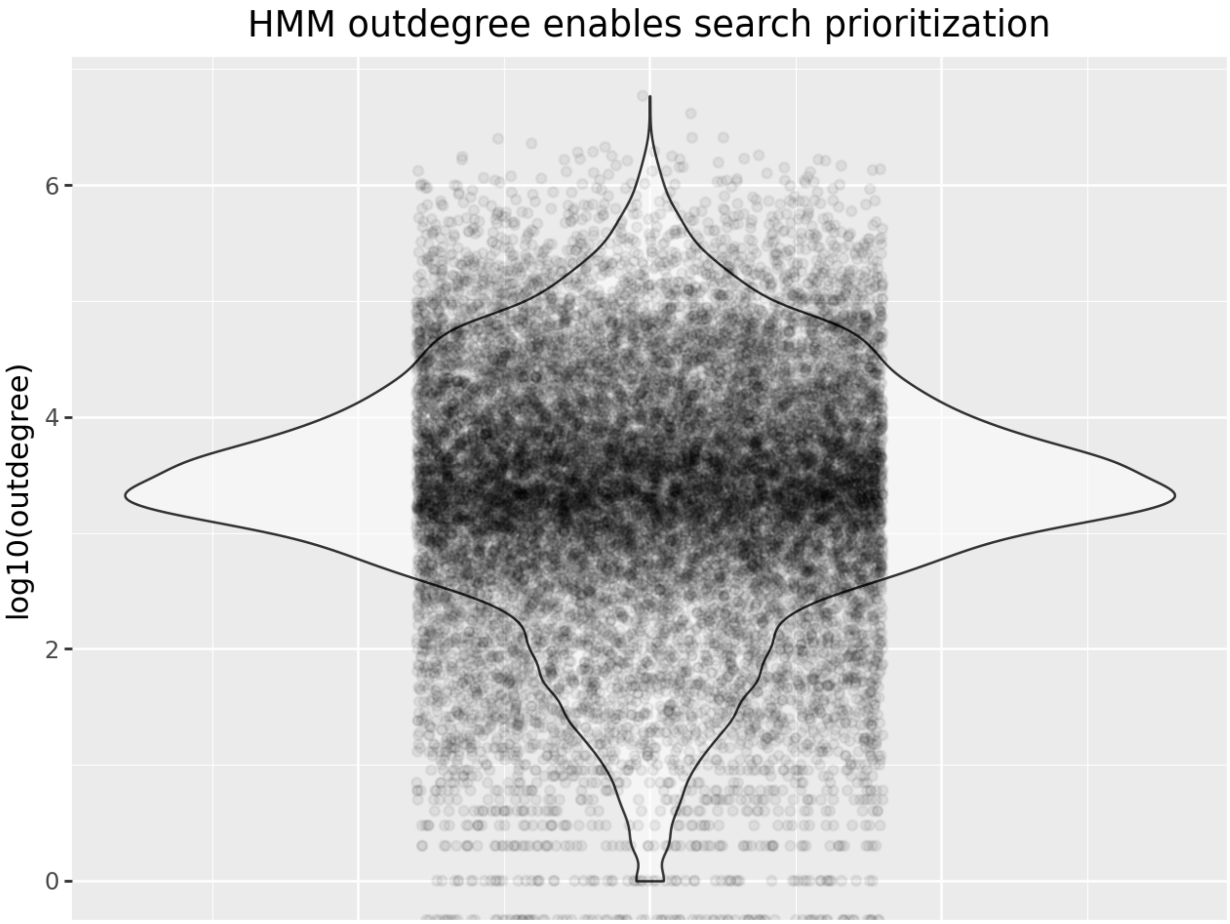
Supplementary Table 1: SocialGene RefSeq database

node label	count
amrfinder	630
antismash	940
assembly	345883
culture_collection	152
goterm	51283
hmm_source	25813
hmm	25566
nucleotide	46179608
parameters	1
pfam	19632
protein	304330794
resfams	123
taxid	2543881
tigrfam_mainrole	19
tigrfam_role	116
tigrfam_subrole	101
tigrfam	4488

relationship type	count
ALTERNATE	3646
ANNOTATES	847850795
ASSEMBLES_TO	46179608
ENCODES	1337412265
FOUND_IN	27874
GO_ANN	6387
IS_A	28045
IS_TAXON	343763
MAINROLE_ANN	116
MMSEQS_30	27681483
MMSEQS_50	54434786
MMSEQS_70	111454401
MMSEQS_90	304330794
NEGATIVELY_REGULATES	2684
PART_OF	6323
POSITIVELY_REGULATES	2682
PROTEIN_TO_GO	35527
REGULATES	3100
ROLE_ANN	3169
SOURCE_DB	25813
SUBROLE_ANN	116
TAXON_PARENT	2543881

The number of nodes and relationships in the base SocialGene RefSeq database. This includes the 343,381 RefSeq genomes along with 2,502 MIBiG BGCs (included under "assembly" and "nucleotide" nodes). Note that these only represent the database as built by the Nextflow pipeline. Additional nodes and relationships mentioned in the manuscript were added through use of add-ons to the SocialGene Python library as they are not suited for import via the Neo4j admin-import command, as they require a running database to make connections to existing nodes.

Supplementary Figure 2: Outdegree distribution of pHMM nodes to non-redundant protein nodes

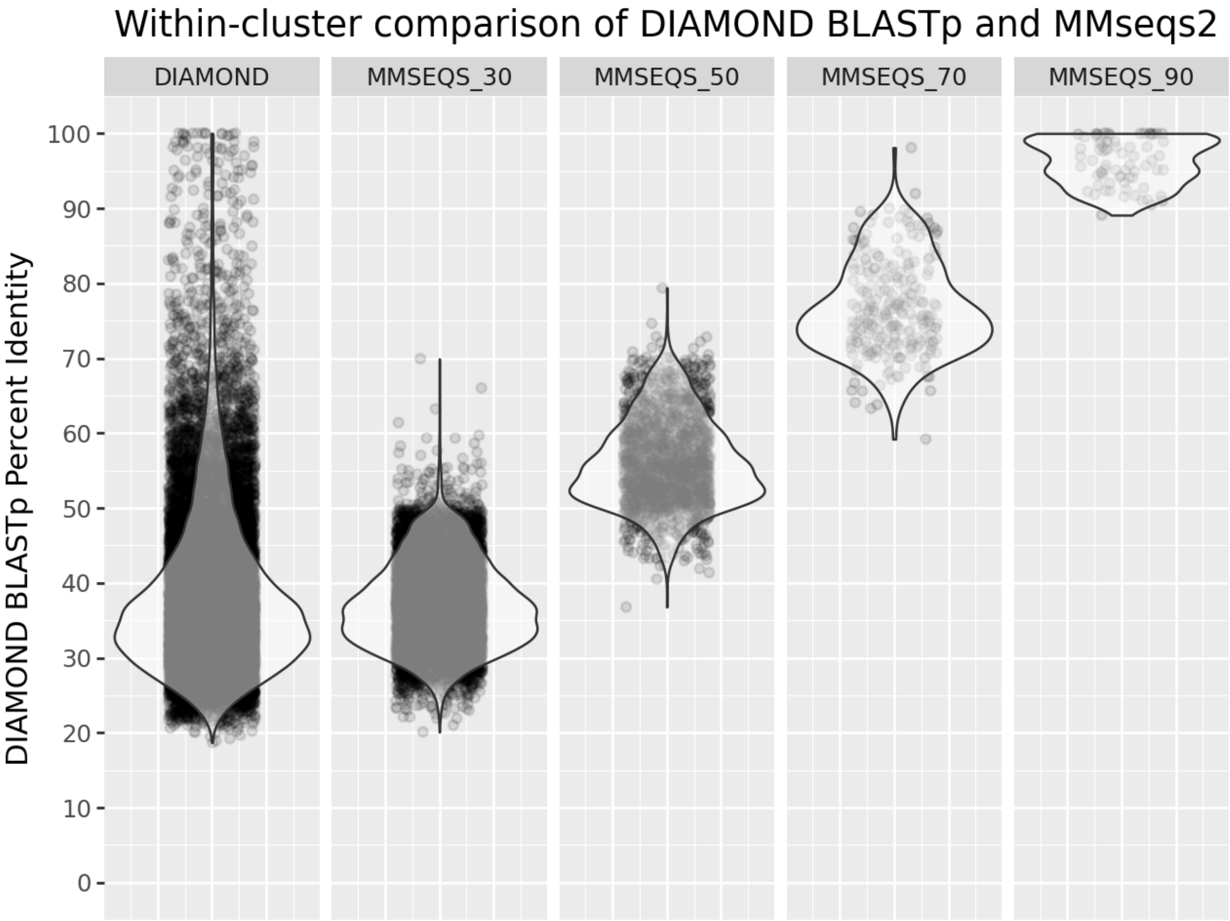


When searching a SocialGene database for similar BGCs one of the prioritization methods within SocialGene's search function is to first rank the pHMM models that annotate the query BGC's proteins based on the number of "ANNOTATES" relationships each of the pHMM model nodes has to non-redundant protein nodes. Prioritizing pHMM models with a lower outdegree reduces the search space and has the side effect that the query domains and proteins that are prioritized are often less common. The figure shows the density of the log10 outdegree of the pHMM models and the 847,850,795 "ANNOTATES" relationships in the SocialGene RefSeq database.

Supplementary Text 1

With a query BGC containing 20 proteins, the algorithm will find all pHMM models annotating the 20 proteins. The proteins are ranked by the ascending sum of their pHMM outdegrees and then a subset of the proteins used for the search. The number of proteins and the number of pHMM models to consider per protein are user-selected variables that are set as absolute or percent values. This allows for a faster search that prioritizes proteins with less frequently seen pHMM annotations and ignores ubiquitous domains and proteins, but can lead to missed BGCs depending on settings and which proteins are present in the query and target BGCs. For example, MIBiG entry BGC0001848 contains 50 proteins and is found in a *Micromonospora* sp. Searching >340,000 genomes for similar BGCs using the top 5 prioritized proteins, as described above, finishes in 2.5 seconds and recovers BGC0001848 and its originating RefSeq genome, among other closely-related BGCs. However, it fails to capture BGC0001850, which is encoded in a *Streptomyces* sp. and produces a similar compound, but only shares 20 of BGC0001848's 50 proteins in a different genetic arrangement; see Braesel et al[1] for detailed analysis of these two clusters. The search function provides the ability to bypass the filters outright, or selectively, for defined query proteins. Future efforts will go towards balancing this search algorithm's efficiency and accuracy.

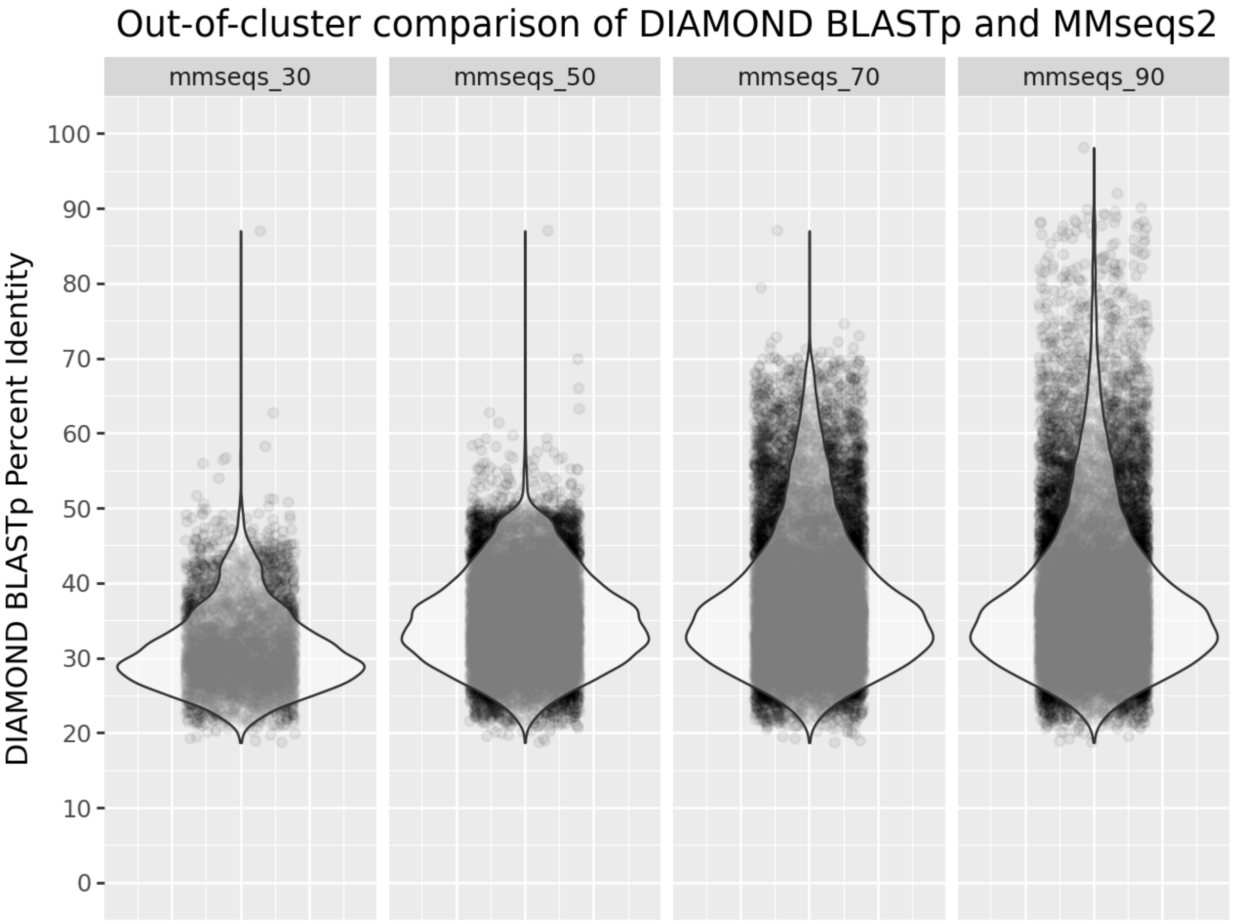
Supplementary Figure 3: Within-cluster comparison of DIAMOND BLASTp and MMseqs2



While the MMseqs2 clustering in SocialGene isn't perfect (possibly due to cascaded clustering being run in SocialGene without cluster reassignment), the MMseqs2 relationships within SocialGene all fall within tolerance of their value (i.e. MMSEQS_50 relationships usually fall within 50%-70% identity. Each point in the figure represents a DIAMOND BLASTp percenet identity score between two within-cluster proteins (e.g. two proteins within the same MMSEQS_90 cluster).

Data shown is from a SocialGene database created with genomes GCF_000009045.1, GCF_000005845.2, GCF_008931305.1 (*Bacillus subtilis* subsp. *subtilis* str. 168, *Escherichia coli* str. K-12 substr. MG1655, and *Streptomyces coelicolor* A3(2); downloaded on June 20, 2024); MMseqs2 clustering in steps of 90, 70, 50, 30 with settings '-c 0.7 --cov-mode 0 --split 1'; all-vs-all DIAMOND BLASTp was run with settings '-k0 --max-hsps 1 --query-cover 70 --subject-cover 70 --block-size 6'.

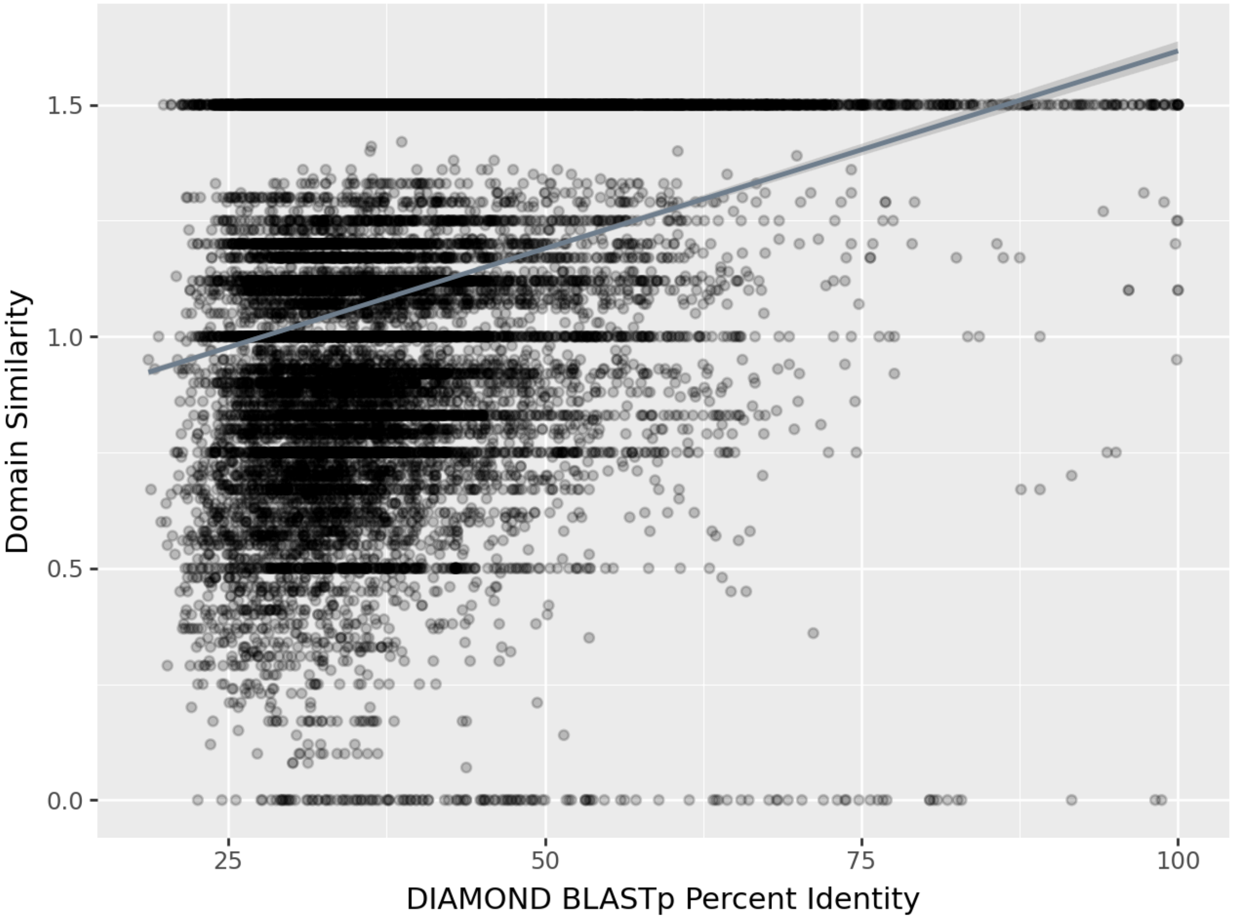
Supplementary Figure 4: Inter-cluster comparisons of DIAMOND BLASTp and MMseqs2



The inter-cluster similarities can sometimes be higher than the MMseqs2 clustering level (e.g. two separate 30% clusters may contain member(s) that share >30%) and should be considered when designing queries/experiments. Each point in the figure represents a DIAMOND BLASTp comparison between two inter-cluster proteins. For example, a point in the 'mmesqs_90' column represents the DIAMOND BLASTp identity of two proteins belonging to different 'mmesqs_90' clusters.

Data shown is from a SocialGene database created with genomes GCF_000009045.1, GCF_000005845.2, GCF_008931305.1 (*Bacillus subtilis* subsp. *subtilis* str. 168, *Escherichia coli* str. K-12 substr. MG1655, and *Streptomyces coelicolor* A3(2); downloaded on June 20, 2024); MMseqs2 clustering in steps of 90,70,50, 30 and settings '-c 0.7 --cov-mode 0 --split 1'; all-vs-all DIAMOND BLASTp was run with settings '-k0 --max-hsps 1 --query-cover 70 --subject-cover 70 --block-size 6'.

Supplementary Figure 5: Lack of correlation between SocialGene's domain similarity and DIAMOND BLASTp identity

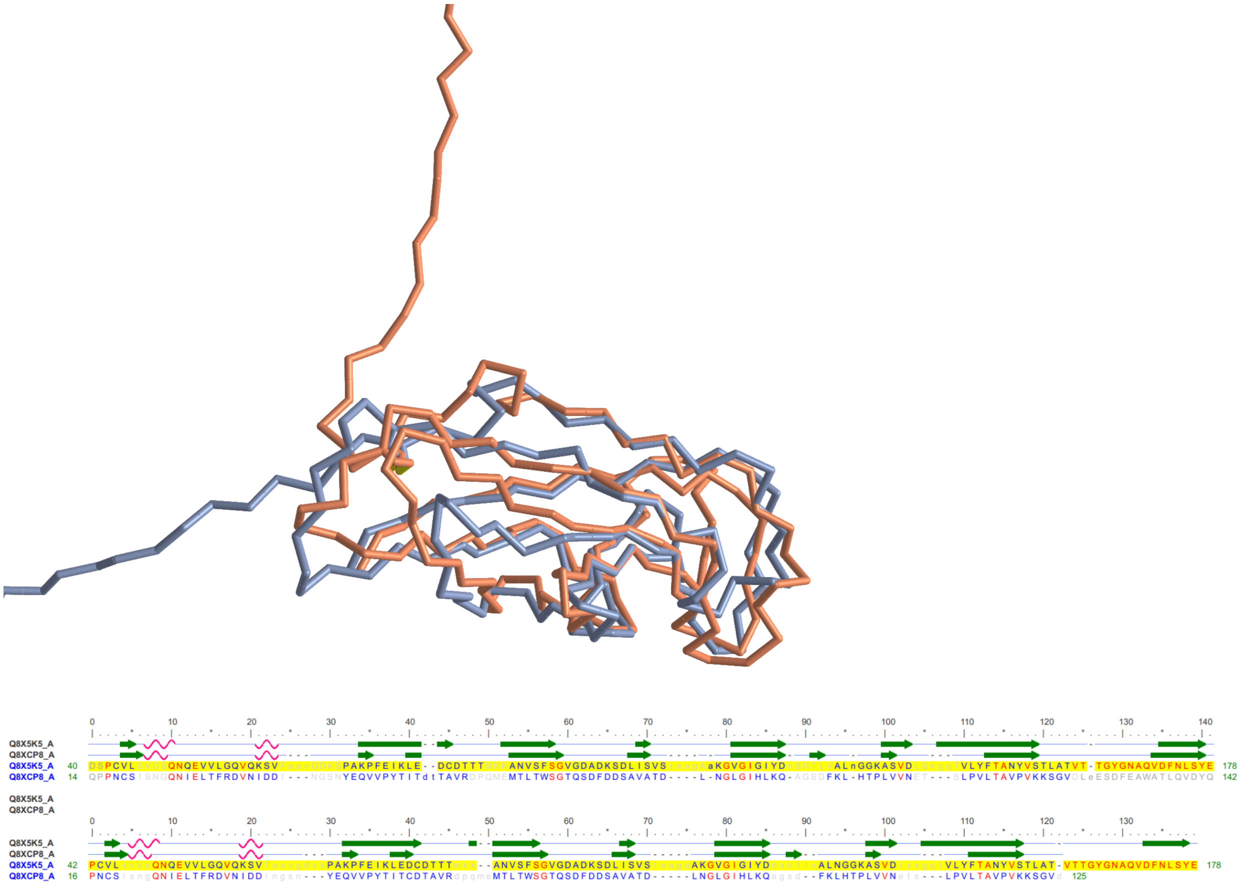


Domain similarity, measured using a combined, weighted Levenshtein and Jaccard similarity score, shows a lack of correlation with sequence alignment scores. This finding is discussed further in the manuscript.

Linear regression: slope 8.6; intercept 29.0; rvalue 0.27; pvalue 0.0; stderr 0.17

Data shown is from a SocialGene database created with genomes GCF_000009045.1, GCF_000005845.2, GCF_008931305.1 (*Bacillus subtilis* subsp. *subtilis* str. 168, *Escherichia coli* str. K-12 substr. MG1655, and *Streptomyces coelicolor* A3(2); downloaded on June 20, 2024); all-vs-all DIAMOND BLASTp was run with settings '-k0 --max-hsps 1 --query-cover 70 --subject-cover 70 --block-size 6'; pHMM databases included "antismash, amrfinder, pfam, resfams, tigrfam".

Supplementary Figure 6: 3D alignment of AlphaFold predicted protein structures

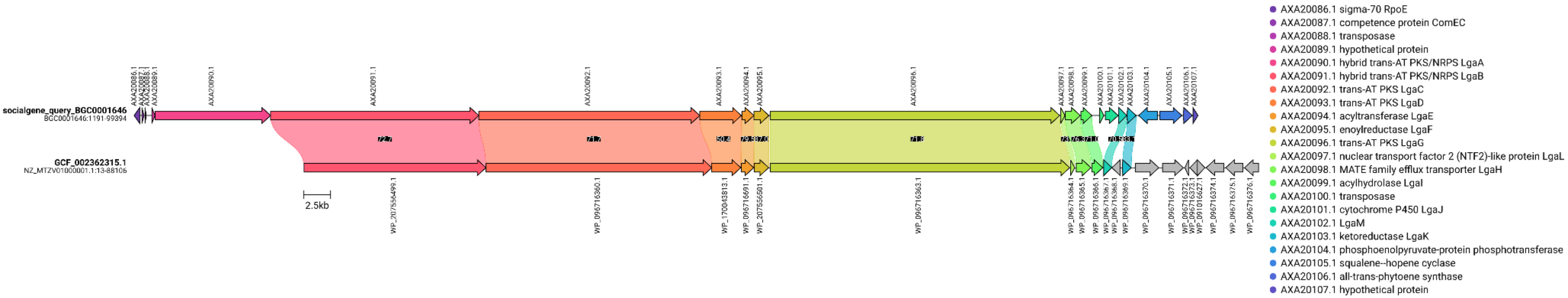

0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
Q8X5K5_A
Q8XCP8_A
Q8X5K5_A 40 DSPCVLSVDSQNQEVVLGQVQKSVFaavGDKSPAKPFEIKLE--DCDTTTMKKANVSFSGVGDADKSDLISVSteagAaKGVGIGIYDnSNTLVALnGGKASVDLSkgqTVLYFTANYVSTLATVT-TGYGNAQVDFNLSYE 178
Q8XCP8_A 14 QPPNCSISNGQNIELTFRDVNIDDI---NGSNYEQVVPYTITdtTAVRDPQMEMTLTWSGTQSDFDDSAVATD----L-NGLGIHLKQ-AGSDFKL-HTPLVVNET---SLPVLTAVPVKKSGVDLeESDFEAWATLQVDYQ 142
Q8X5K5_A
Q8XCP8_A
0 10 20 30 40 50 60 70 80 90 100 110 120 130
Q8X5K5_A
Q8XCP8_A
Q8X5K5_A 42 PCVLsvdsQNQEVVLGQVQKSVfaavgdksPAKPFEIKLEDCDTTTmkk--ANVSFSGVGDADKSDLISVSteagaAKGVGIGIYDnsntlvALNGGKASVDlskgqtVLYFTANYVSTLAT-VTTGYGNAQVDFNLSYE 178
Q8XCP8_A 16 PNCSisngQNIELTFRDVNIDDingsn---YEQVVPYTITCDTAVRdpqmeMTLTWSGTQSDFDDSAVATD-----LNGLGIHLKQagsd--FKLHTPLVVNets---LPVLTAVPVKKSGVd 125

Alignment of the AlphaFold[2] predicted 3D protein structures (AlphaFold DB version 2022-11-01) using TM-align[3] through NCBI-hosted iCn3D[4,5] showed that, while the proteins have highly dissimilar AA sequences, they have similar predicted 3D structures (RMSD: 2.487 Å, TM-score: 0.7134; approximately 15-20% of the proteins' residues remain unfolded).
Structures for proteins Q8X5K5 (orange, with unfolded region pointing up) and Q8XCP8 (blue, with unfolded region pointing left). The two proteins share such low sequence identity that they are not aligned by BLASTp's default settings, but are both annotated by a single PFAM pHMM, PF00419.23. The aligned, predicted 3D protein structures can be viewed at: https://structure.ncbi.nlm.nih.gov/icn3d/share.html?Ei8f9WLdzgqaRQXv7

Supplementary Text 2:

A nearly-perfect BLASTp alignment doesn't necessitate similar pHMM annotation. For example, UniProtKB A0A0H3JI96 and A0A0H3JGM8 are phage tail proteins encoded in the *Escherichia coli* O157:H7 genome. While BLASTp alignment revealed matches in 233 of 238 positions (97.9% identity), only a third of their pHMM annotations overlapped. Inspecting the PFAM pHMM annotations for these proteins through UniProt's web service (on 05-01-2023) revealed A0A0H3JGM8 was annotated by model PF13927 and A0A0H3JI96 by a different model, PF07679. However, aligning PFAM models with pHMMscan using European Bioinformatics Institute's (EBI's) pHMMerWeb version 2.41.2 resulted in A0A0H3JGM8 being annotated by models PF13927, PF13895, and PF07679 (though only PF13927 was reported, as it was chosen to represent the PFAM clan) and A0A0H3JI96 being annotated by model PF07679. The discrepancy between UniProt and EBI's annotation of A0A0H3JGM8 was likely due to different post-processing in choosing PFAM clan members. Currently SocialGene doesn't prune PFAM pHMM annotations based on PFAM clan membership and so it reported A0A0H3JGM8 as annotated by PF13927, PF13895, and PF07679; and A0A0H3JI96 as annotated by PF07679, resulting in them sharing a single annotation, of three, for a similarity score of 0.33. Future versions of SocialGene may work to address a reproducible method for pruning PFAM annotations by clan. Nevertheless, it remains that pHMM annotation can be disrupted even at high BLASTp identities and, at the time of writing, comparing PFAM annotations between any of EBI's pHMMerWeb, UniProt, and SocialGene could lead to missing proteins with similar annotations. In this case, comparing UniProt annotations to EBI's pHMMerWeb would have resulted in missing the similar proteins, whereas SocialGene didn't, due to consistent pHMM annotation.

Supplementary Figure 7: Recovery of a known lagriamide B BGC from *Paraburkholderia acidicola*, using the Lagriamide A producing BGC (BGC0001646) as the search query


socialgene_query_BGC0001646
BGC0001646:1191-99394
GCF_002362315.1
NZ_MTZV01000001.1:13-88106
2.5kb
AXA20086.1
AXA20087.1
AXA20088.1
AXA20089.1
AXA20090.1
AXA20091.1
AXA20092.1
AXA20093.1
AXA20094.1
AXA20095.1
AXA20096.1
AXA20097.1
AXA20098.1
AXA20099.1
AXA20100.1
AXA20101.1
AXA20102.1
AXA20103.1
AXA20104.1
AXA20105.1
AXA20106.1
AXA20107.1
72.7
71.7
50.4
71.8
WP_207556499.1
WP_096716360.1
WP_170043813.1
WP_096716691.1
WP_207556501.1
WP_096716363.1
WP_096716364.1
WP_096716365.1
WP_096716366.1
WP_096716367.1
WP_096716368.1
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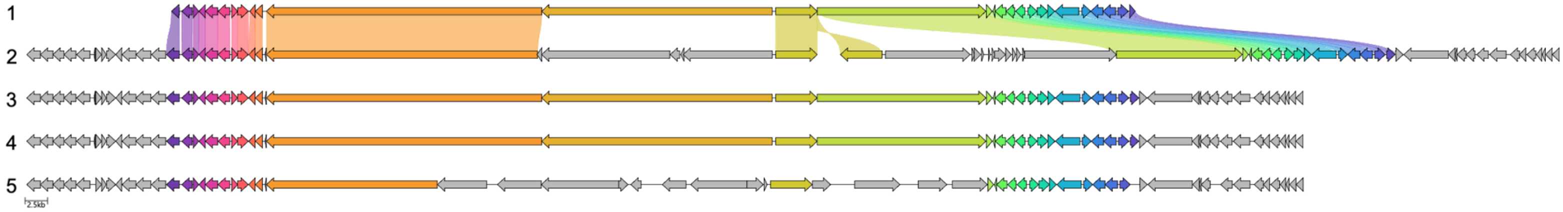
WP_096716372.1
WP_096716373.1
WP_091016627.1
WP_096716374.1
WP_096716375.1
WP_096716376.1
● AXA20086.1 sigma-70 RpoE
● AXA20087.1 competence protein ComEC
● AXA20088.1 transposase
● AXA20089.1 hypothetical protein
● AXA20090.1 hybrid trans-AT PKS/NRPS LgaA
● AXA20091.1 hybrid trans-AT PKS/NRPS LgaB
● AXA20092.1 trans-AT PKS LgaC
● AXA20093.1 trans-AT PKS LgaD
● AXA20094.1 acyltransferase LgaE
● AXA20095.1 enoylreductase LgaF
● AXA20096.1 trans-AT PKS LgaG
● AXA20097.1 nuclear transport factor 2 (NTF2)-like protein LgaL
● AXA20098.1 MATE family efflux transporter LgaH
● AXA20099.1 acylhydrolase LgaI
● AXA20100.1 transposase
● AXA20101.1 cytochrome P450 LgaJ
● AXA20102.1 LgaM
● AXA20103.1 ketoreductase LgaK
● AXA20104.1 phosphoenolpyruvate-protein phosphotransferase
● AXA20105.1 squalene--hopene cyclase
● AXA20106.1 all-trans-phytoene synthase
● AXA20107.1 hypothetical protein

The SocialGene BGC search was run against the RefSeq SocialGene database using the following parameters: use_neo4j_precalc: True; assemblies_must_have_x_matches: 0.6; nucleotide_sequences_must_have_x_matches: 0.6; gene_clusters_must_have_x_matches: 0.6; break_bgc_on_gap_of: 20000; target_bgc_padding: 10000; max_domains_per_protein: 3; max_outdegree: 300000; max_query_proteins: 10; scatter: True; locus_tag_bypass_list: None; protein_id_bypass_list: None; only_culture_collection: False; frac: 0.75; run_async: True; analyze_with: "blastp"

Additional partial match, lower-scoring, target BGCs were removed for figure clarity. Both a high resolution and interactive version of the plot are available in the archived manuscript's repository (see manuscript's Data and Code Availability section).

Supplementary Figure 8: Fragmented rapamycin BGCs found by SocialGene BGC search



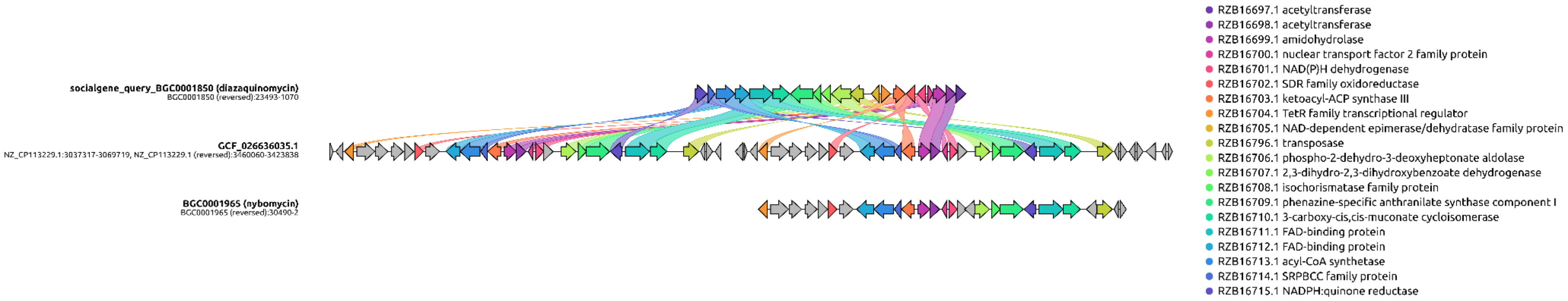
	Assembly	Org	Sequencing	Assembly	Gene Calling
1	BGC0001040	University of Cambridge	ABI 373A	Staden Package	BLAST/FASTA
2	GCF_014205315.1	DOE Joint Genome Institute	PacBio	Flye v. 2.6	PGAP 6.6
3	GCF_003675955.1	Novartis AG	PacBio RSII	HGAP v. DEC-2014	PGAP 6.4
4	GCF_024298965.1	Korea University	PacBio RSII; Illumina NovaSeq	HGAP v. 2.3	PGAP 6.4
5	GCF_000418455.1	University of Kaiserslautern	454	GS De Novo Assembler (v 2.8) program (Roche) v. 2.8	PGAP 6.4

All five of the above sequences derive from separate sequencing efforts of the same type strain, *Streptomyces rapamycinicus* DSM 41530/NRRL 549. Despite being the same organism, the rapamycin BGC in assembly 2 is split across two contigs and has fragmented polyketide synthase genes. Additionally, assembly 5 contains fragmented polyketide synthase genes. Despite this, SocialGene's search function was able to recover these BGCs when BGC0001040 was used as input.

The search was run against the RefSeq SocialGene database using the following parameters: use_neo4j_precalc=True; assemblies_must_have_x_matches=0.4; nucleotide_sequences_must_have_x_matches=0.4; gene_clusters_must_have_x_matches=0.4; break_bgc_on_gap_of=20000; target_bgc_padding=10000; max_domains_per_protein=3; max_outdegree=1000000; max_query_proteins=5; scatter=False; locus_tag_bypass_list=None; protein_id_bypass_list=None; only_culture_collection=False; frac=0.75; run_async=True; analyze_with="blastp"

There were additional assemblies with results but which were removed for figure clarity.

Supplementary Figure 9: SocialGene BGC search recovering multiple BGC integrations

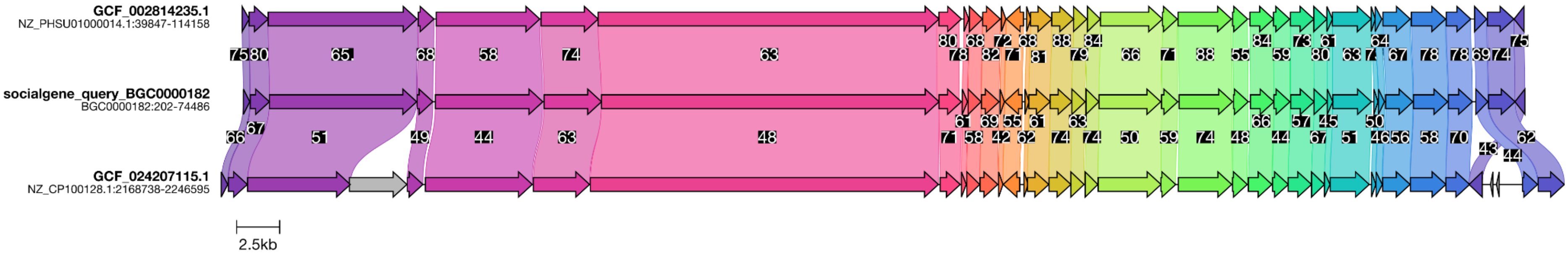

socialgene_query_BGC0001850 (diazaquinomycin)
BGC0001850 (reversed):23493-1070
GCF_026636035.1
NZ_CP113229.1:3037317-3069719, NZ_CP113229.1 (reversed):3460060-3423838
BGC0001965 (nybomycin)
BGC0001965 (reversed):30490-2
RZB16697.1 acetyltransferase
RZB16698.1 acetyltransferase
RZB16699.1 amidohydrolase
RZB16700.1 nuclear transport factor 2 family protein
RZB16701.1 NAD(P)H dehydrogenase
RZB16702.1 SDR family oxidoreductase
RZB16703.1 ketoacyl-ACP synthase III
RZB16704.1 TetR family transcriptional regulator
RZB16705.1 NAD-dependent epimerase/dehydratase family protein
RZB16796.1 transposase
RZB16706.1 phospho-2-dehydro-3-deoxyheptonate aldolase
RZB16707.1 2,3-dihydro-2,3-dihydroxybenzoate dehydrogenase
RZB16708.1 isochorismatase family protein
RZB16709.1 phenazine-specific anthranilate synthase component I
RZB16710.1 3-carboxy-cis,cis-muconate cycloisomerase
RZB16711.1 FAD-binding protein
RZB16712.1 FAD-binding protein
RZB16713.1 acyl-CoA synthetase
RZB16714.1 SRPBCC family protein
RZB16715.1 NADPH:quinone reductase

While using BGC0001850 (first BGC in figure, encodes for diazaquinomycin) to spot-check the results of querying all MIBiG BGCs against the RefSeq SocialGene database it was noticed that two assemblies had multiple copies of a similar BGC to BGC0001850. These BGCs were most similar to another MIBiG entry, BGC0001965 (bottom BGC in figure), which encodes for nybomycin, a chemical analog of diazaquinomycin. Further inquiry revealed the genome assembly GCF_026636035.1 to be a *Streptomyces albidoflavus* strain engineered for the overproduction of nybomycin[6] (middle BGC in figure). The second assembly recovered (not shown) was GCF_026210455.1, the BAC 4N24 plasmid donor from the same study [6].

The search was run against the RefSeq SocialGene database using the following parameters:
use_neo4j_precalc: True; assemblies_must_have_x_matches: 0.7; nucleotide_sequences_must_have_x_matches: 0.7; gene_clusters_must_have_x_matches: 0.7; break_bgc_on_gap_of: 10000; target_bgc_padding: 20000; max_domains_per_protein: 3; max_outdegree: 1000000; max_query_proteins: 10; scatter: False; locus_tag_bypass_list: None; protein_id_bypass_list: None; only_culture_collection: False; frac: 0.75; run_async: True; analyze_with: 'blastp'

There were additional assemblies with results but which were removed for figure clarity.

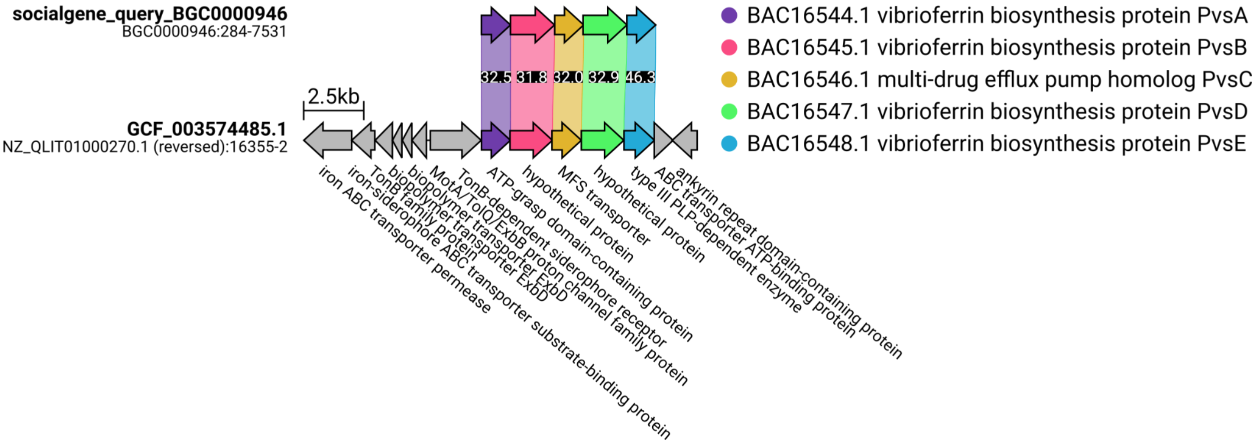
Supplementary Figure 10: Putative pseudomonic acid BGCs



MIBiG BGC0000182 is a pseudomonic acid BGC from *Pseudomonas fluorescens*. When using SocialGene to search for related BGCs in the RefSeq SocialGene database two genomes had BGCs highly syntenic to BGC0000182 but with relatively low individual protein identities (black labels between homologous BGC genes). GCF_002814235 is *Pseudomonas* sp. QS1027 and GCF_024207115 is *Chromobacterium* sp. IIBBL 290-4 which falls in a separate taxonomic class. Both a high resolution and interactive version of the plot are available in the archived manuscript's repository (see manuscript's Data and Code Availability section).

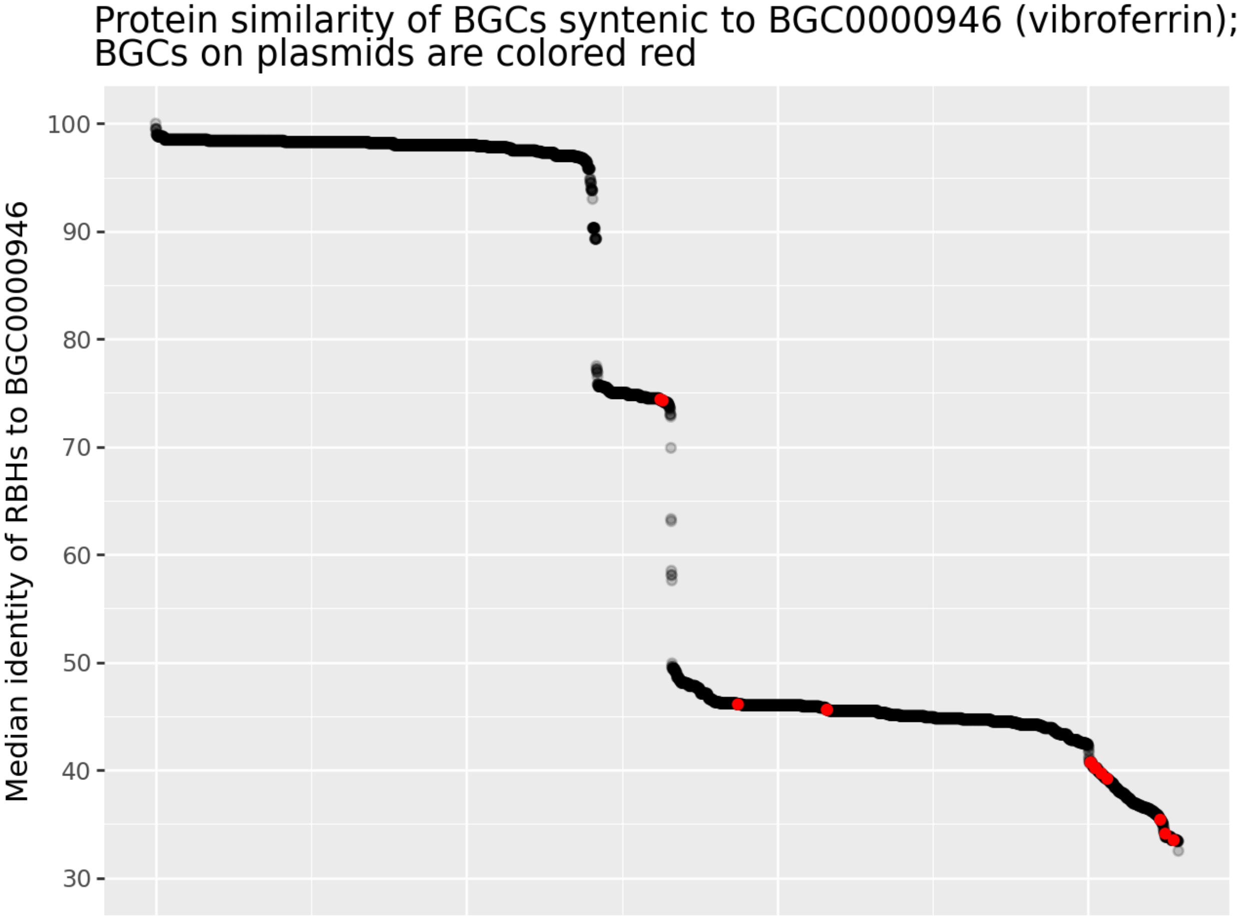
The *Chromobacterium* BGC is available in antiSMASH DB[7]:
https://antismash-db.secondarymetabolites.org/output/GCF_024207115.1/index.html#r1c3

Supplementary Figure 11: Target BGC with the lowest median BLASTp similarity (34.1) to the vibrioferrin BGC, BGC0000946


socialgene_query_BGC0000946
BGC0000946:284-7531
32.5
31.8
32.0
32.9
46.3
2.5kb
GCF_003574485.1
NZ_QLIT01000270.1 (reversed):16355-2
iron ABC transporter permease
iron-siderophore ABC transporter substrate-binding protein
TonB family protein
biopolymer transporter ExbD
biopolymer transporter ExbD
MotA/TolQ/ExbB proton channel family protein
TonB-dependent siderophore receptor
ATP-grasp domain-containing protein
hypothetical protein
MFS transporter
hypothetical protein
type III PLP-dependent enzyme
ABC transporter ATP-binding protein
ankyrin repeat domain-containing protein
● BAC16544.1 vibrioferrin biosynthesis protein PvsA
● BAC16545.1 vibrioferrin biosynthesis protein PvsB
● BAC16546.1 multi-drug efflux pump homolog PvsC
● BAC16547.1 vibrioferrin biosynthesis protein PvsD
● BAC16548.1 vibrioferrin biosynthesis protein PvsE

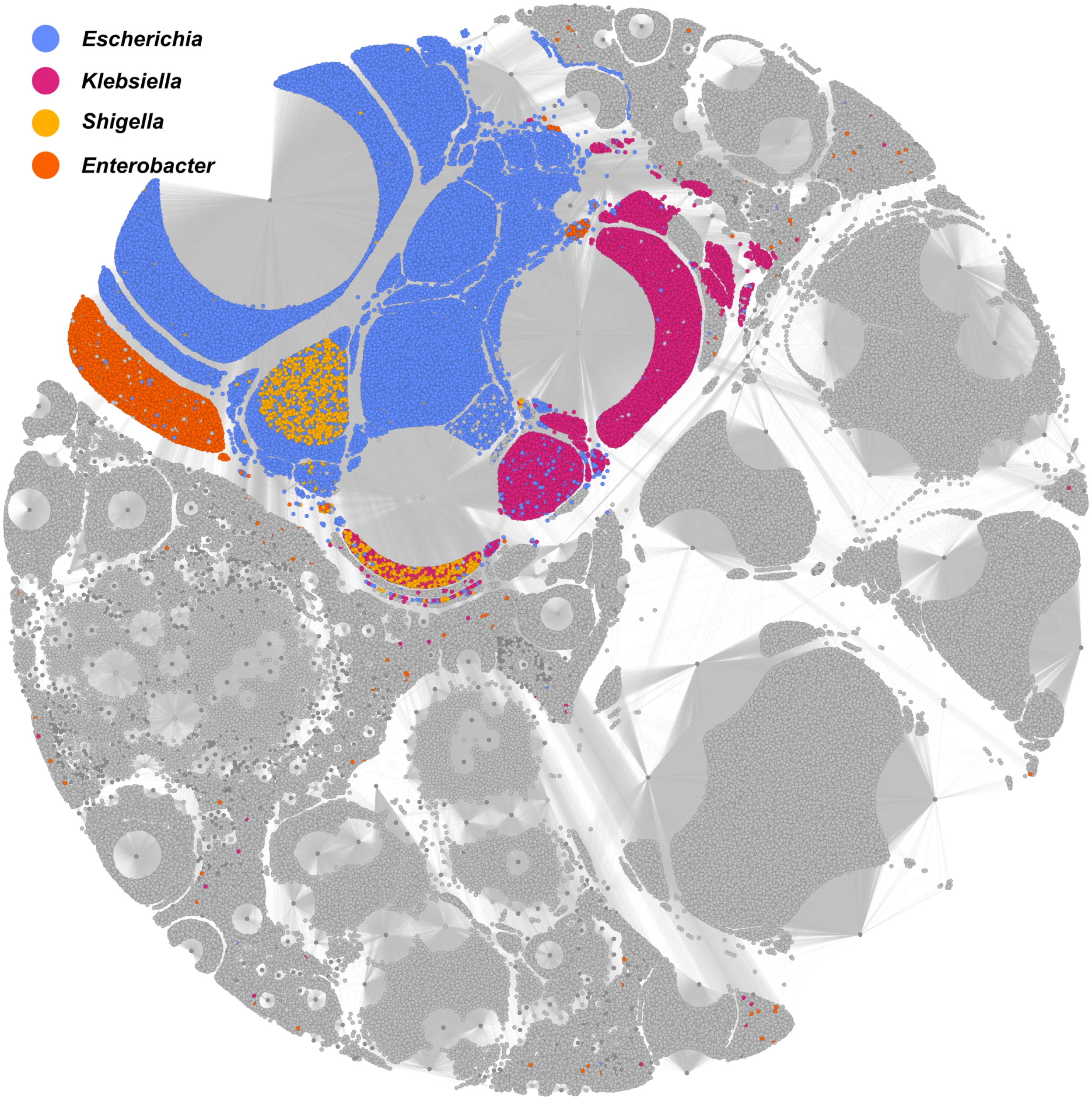
When searching for homologous gene clusters to BGC0000946 (vibrioferrin), the lowest median RBH identity of 32.5% belonged to *Facilibium subflavum* (GCF_003574485.1; NZ_QLIT01000270.1). The legend proteins and colors are derived from BGC0000946. The surrounding gene neighborhood suggests that the BGC is involved in metal homeostasis.

Supplementary Figure 12: Putative vibrioferrin BGCs located on putative plasmids



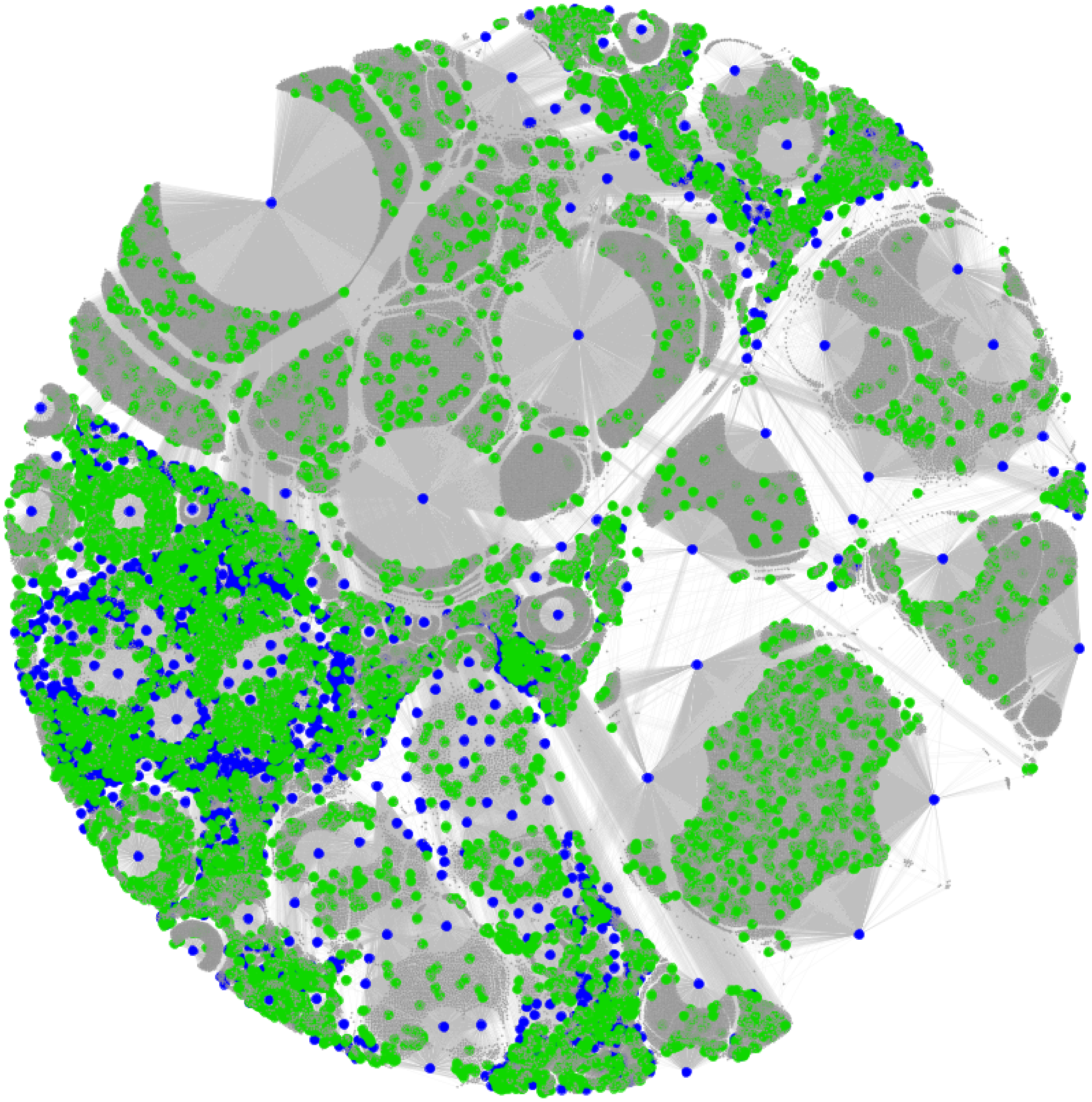
We were curious if there would be a tendency for BGCs near the cliffs to be seen on plasmids which might signal that a genetic transfer event occurred. This figure is identical to Fig. 4 except that for each BGC the nucleotide sequence identifier was used to query the SocialGene database and return results where the sequence was annotated in RefSeq as occurring on a plasmid, these are highlighted as red points. Though further study is needed, it is interesting that most BGCs occurring on plasmids are found after the first and second cliffs. Further studies could use SocialGene to find and cluster transposes flanking the BGCs using the MMSeqs2 clusters.

Supplementary Figure 13: Connecting genomes to BGCs with MMseqs2



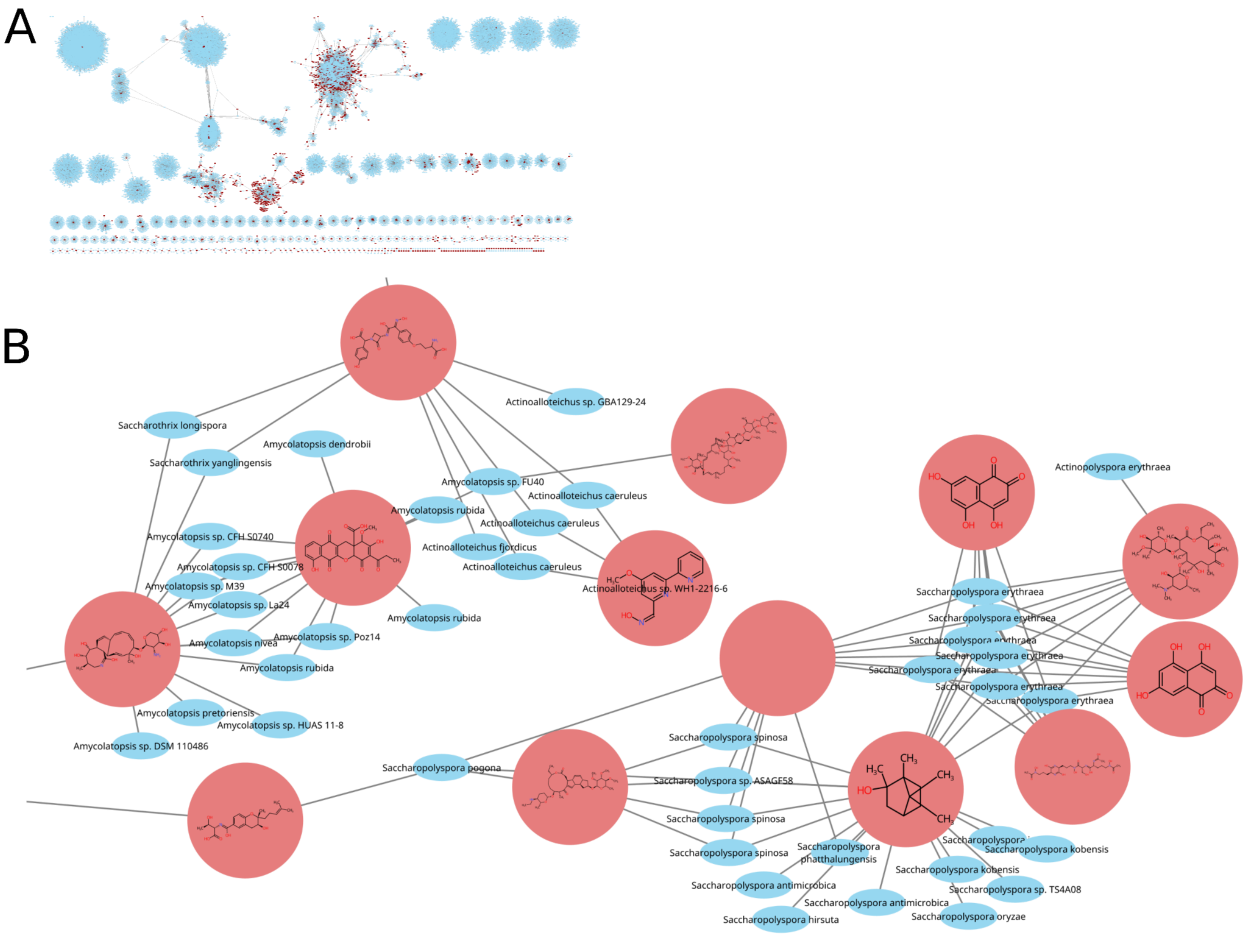
The full subgraph mentioned in Fig 5. Using a single Neo4j Cypher statement, new links (edges between nodes) were created between MIBiG BGCs (nodes) and genomes assemblies (nodes). New links were created where an assembly contained an antiSMASH predicted BGC whose proteins were at least 70% similar to at least 70% of a MIBiG BGC. The new subgraph consists of 366,404 relationships between 1,721 MIBiG BGCs and 158,479 genome assemblies.

Supplementary Figure 14: Connecting genomes to BGCs with MMseqs2 and highlighting culture collection organisms



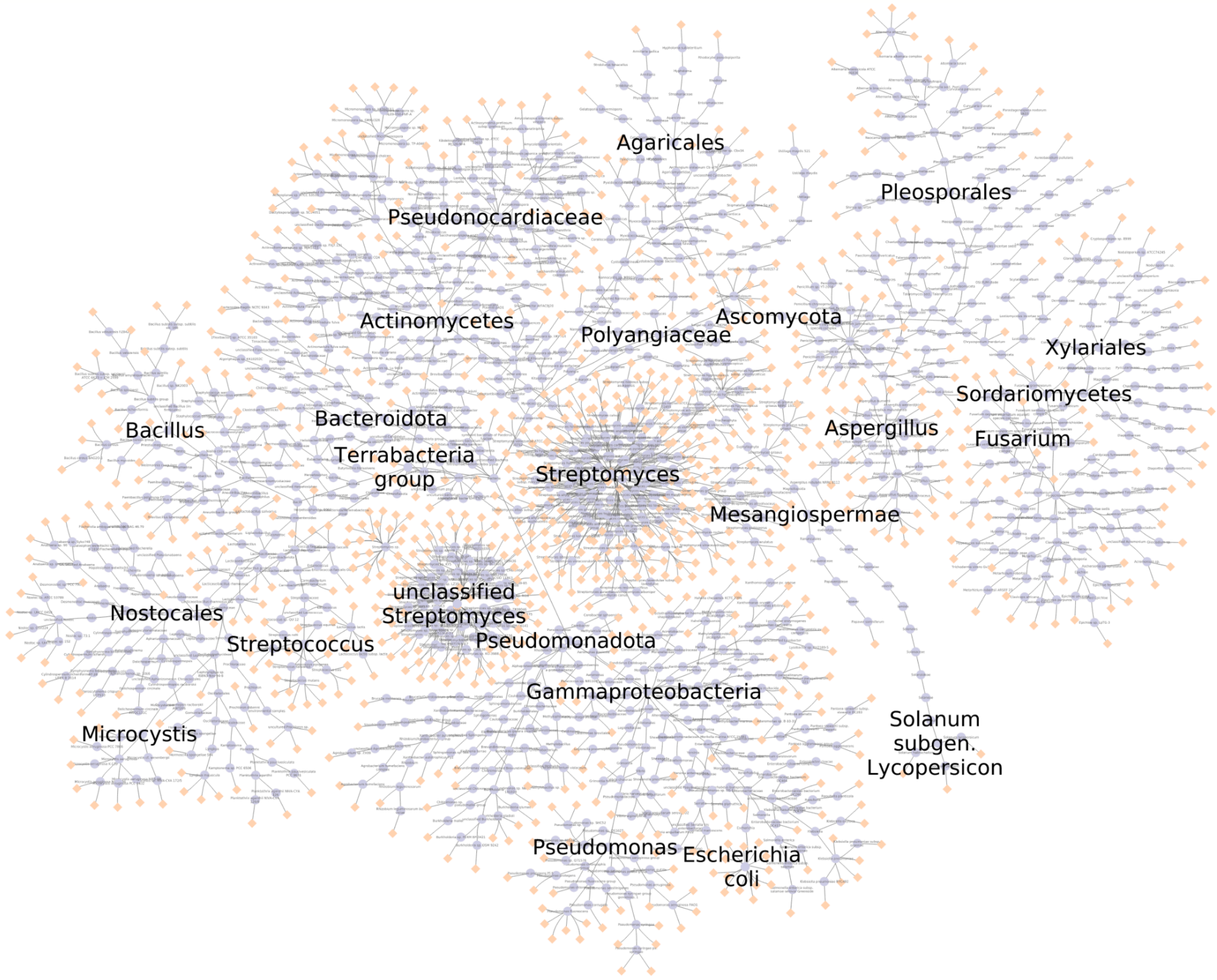
The same nodes and relationships as in Supplementary Fig. 13. The green nodes represent genome assemblies of strains that could be found in a strain collection (e.g. NRRL, ATCC, DSMZ, etc.); blue nodes represent MIBiG BGCs; gray nodes represent other genome assemblies. Note that in small scale (in this document) it isn't possible to faithfully represent the 160,200 nodes of the graph (i.e. it is overplotted). However, especially when displayed interactively, such analyses allow researchers to quickly identify strains that are available for testing their hypotheses.

Supplementary Figure 15: Connecting genomes to BGCs with MMseqs2; displaying chemistry in Cytoscape


A
B
Saccharothrix longispora
Saccharothrix yanglingensis
Amycolatopsis dendrobii
Actinoalloteichus sp. GBA129-24
Amycolatopsis sp. FU40
Actinoalloteichus caeruleus
Amycolatopsis rubida
Actinoalloteichus caeruleus
Actinoalloteichus fjordicus
Actinoalloteichus caeruleus
Actinoalloteichus sp. WH1-2216-6
Amycolatopsis sp. CFH S0740
Amycolatopsis sp. CFH S0078
Amycolatopsis sp. M39
Amycolatopsis sp. La24
Amycolatopsis rubida
Amycolatopsis nivea
Amycolatopsis sp. Poz14
Amycolatopsis rubida
Amycolatopsis pretoriensis
Amycolatopsis sp. HUAS 11-8
Amycolatopsis sp. DSM 110486
Actinopolyspora erythraea
Saccharopolyspora erythraea
Saccharopolyspora erythraea
Saccharopolyspora erythraea
Saccharopolyspora erythraea
Saccharopolyspora erythraea
Saccharopolyspora erythraea
Saccharopolyspora erythraea
Saccharopolyspora pogona
Saccharopolyspora spinosa
Saccharopolyspora sp. ASAGF58
Saccharopolyspora spinosa
Saccharopolyspora spinosa
Saccharopolyspora phatthalungensis
Saccharopolyspora
Saccharopolyspora kobensis
Saccharopolyspora kobensis
Saccharopolyspora sp. TS4A08
Saccharopolyspora antimicrobica
Saccharopolyspora antimicrobica
Saccharopolyspora hirsuta
Saccharopolyspora oryzae

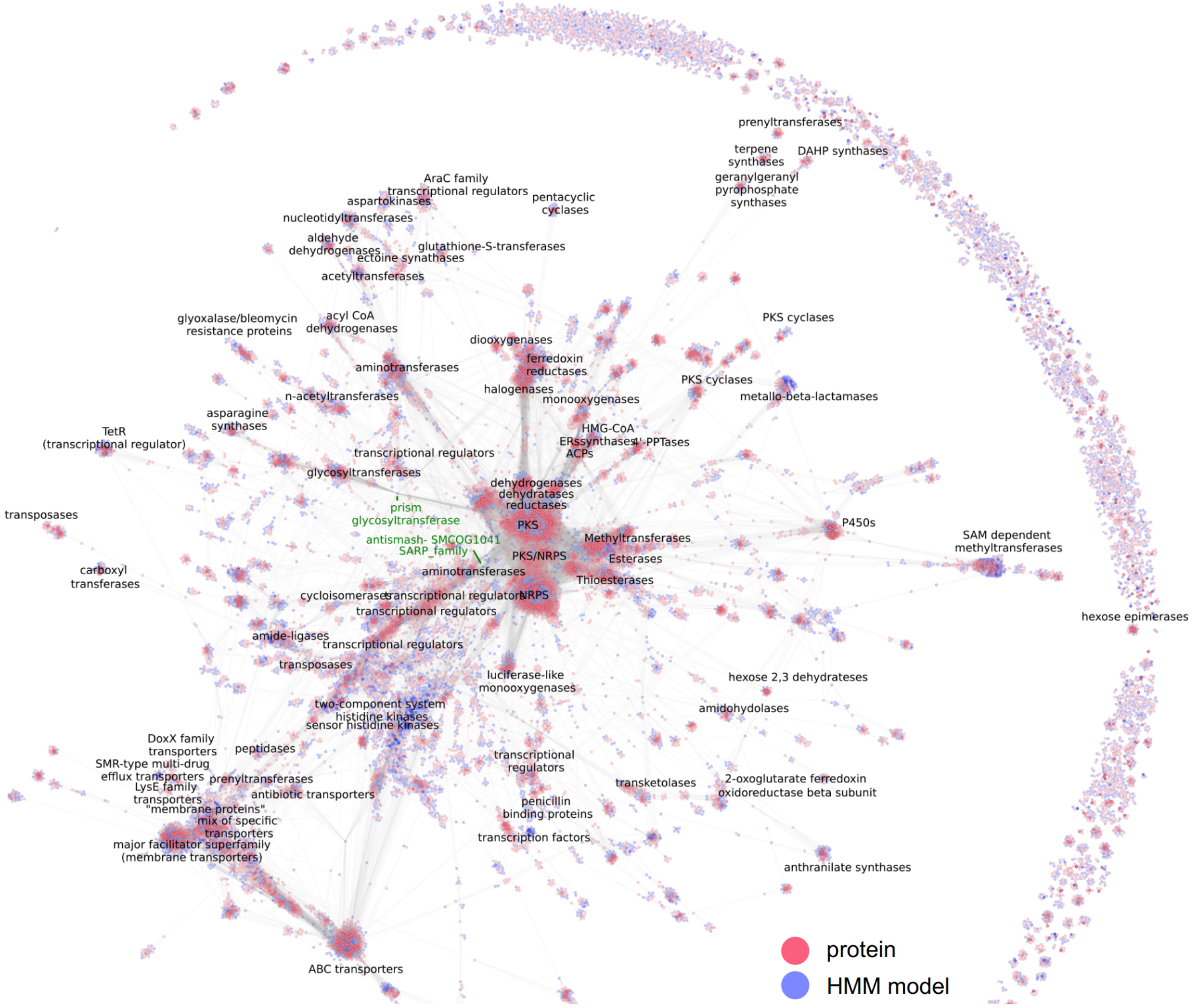
The same nodes and relationships as in Supplementary Figs. 13,14, but imported into Cytoscape directly from the database, using the Cytoscape Neo4j plugin. All MIBiG BGCs were connected to any RefSeq genome assembly which contained at least one antiSMASH 7 annotated region with proteins that matched at least 70% of the MIBiG BGC at 70% or greater identity. Protein similarity (identity) was determined by traversing MMseqs2 cluster relationships within the database (MMSEQS_90 and MMSEQS_70 edges). Panel A is a partial view of the resulting RefSeq assemblies and MIBiG BGCs (160,200 nodes) and the newly formed connecting edges. Not all nodes and relationships are displayed, due to limits of Cytoscape. Panel B is a random, zoomed-in subset of panel A, with genomes labeled with the organism's taxonomic names and MIBiG BGCs labeled by their associated chemical structures, where available, using the chemviz2 Cytoscape plugin.

Supplementary Figure 16: Taxonomic placement of all MIBiG BGCs



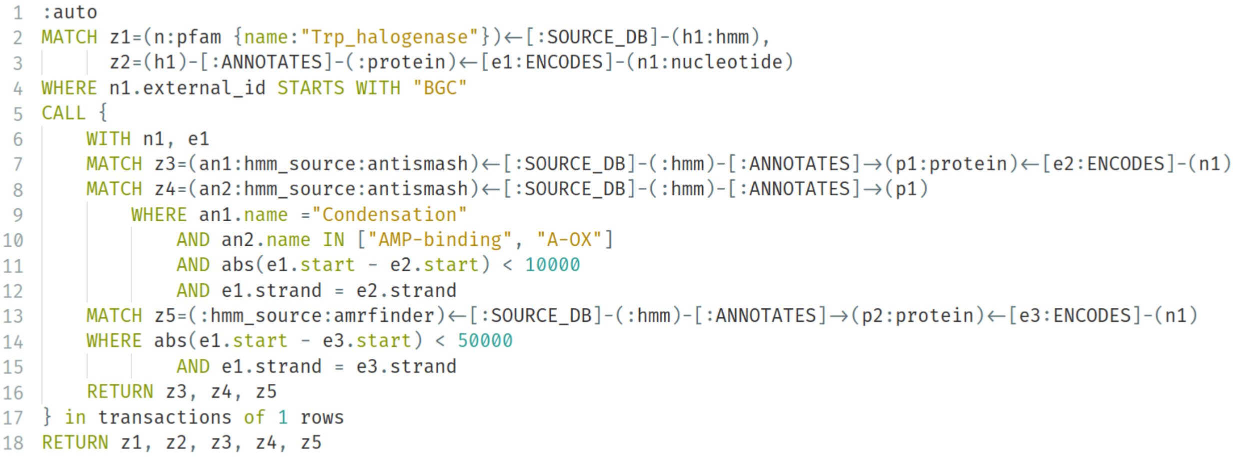
SocialGene's Nextflow workflow allows the incorporation of NCBI taxonomy into the resulting graph database. Here we show the taxonomic placement of all MIBiG BGCs within a SocialGene graph database. Blue nodes (circles) represent individual taxa from NCBI taxonomy and terminal yellow nodes represent MIBiG BGCs. Relationships (lines) between blue nodes represent taxonomic hierarchy (e.g. species, genus, family, etc.). Choice taxa were labeled in order to orient the reader. Combining analyses like this with Cytoscape chemistry plugins allows users to visualize chemical distribution across taxonomy, as does in-database chemical similarity and other cheminformatics.

Supplementary Figure 17: MIBiG protein and pHMM graph



A minimal SocialGene database was created containing all MIBIG BGCs. Using Neo4j Cypher's "apoc.export.graphml.query" function proteins, pHMM models, and the links connecting the two were exported to a graphml. The graphml file was then imported into Gephi and arranged with ForceAtlas2[8]. Clusters of proteins and pHMM models were manually evaluated and found to be largely homogenous in function (based on protein names/descriptions). A subset of clusters were labeled according to their consensus protein name or class.
An interactive version of the graph is available at https://socialgene.github.io/mibigmap.

Supplementary Figure 18: Targeted drug discovery cypher query



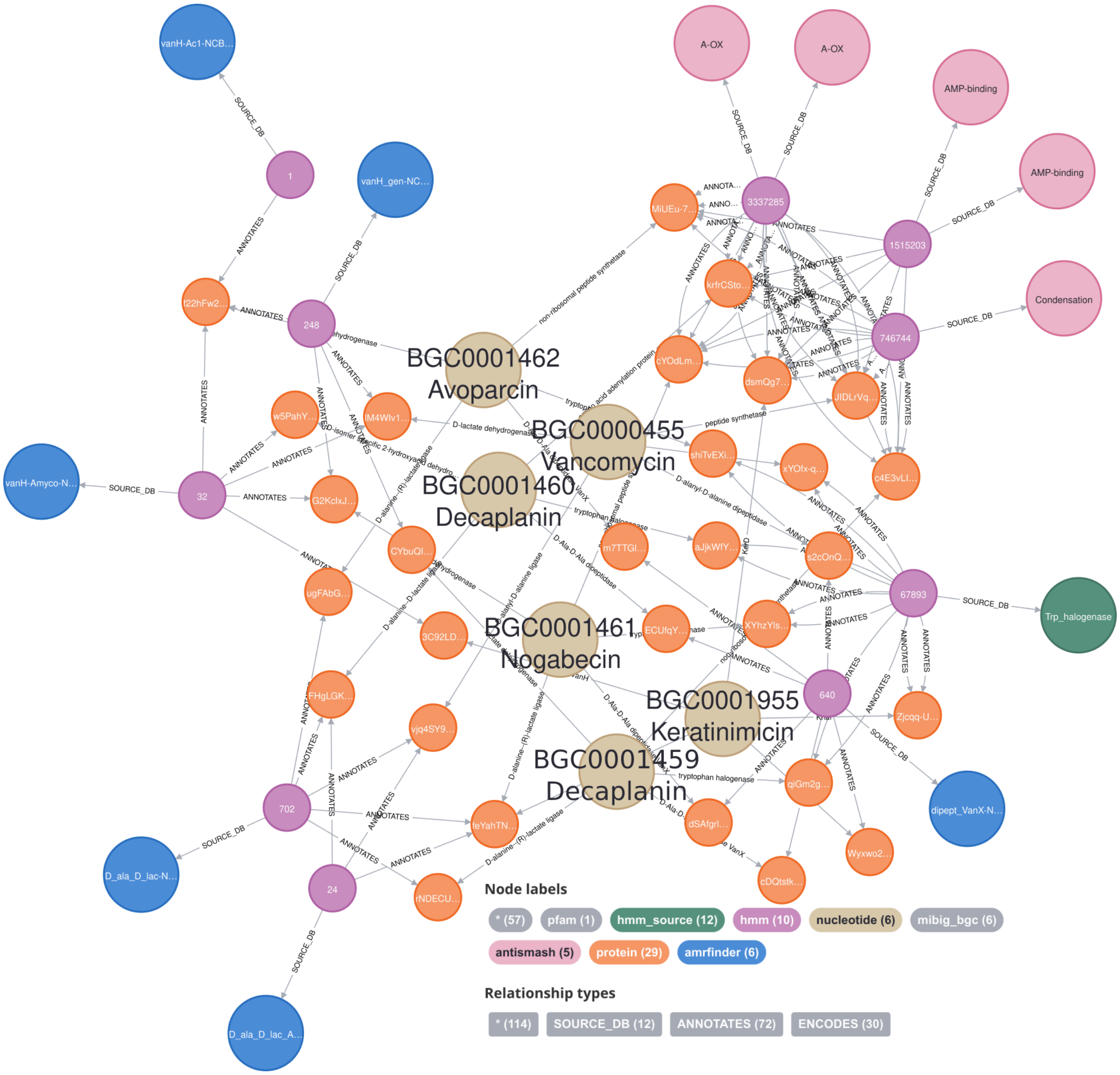
```
:auto
MATCH z1=(n:pfam {name:"Trp_halogenase"})<-[:SOURCE_DB]-(h1:hmm),
      z2=(h1)-[:ANNOTATES]-(:protein)<-[e1:ENCODES]-(n1:nucleotide)
WHERE n1.external_id STARTS WITH "BGC"
CALL {
    WITH n1, e1
    MATCH z3=(an1:hmm_source:antismash)<-[:SOURCE_DB]-(:hmm)-[:ANNOTATES]->(p1:protein)<-[e2:ENCODES]-(n1)
    MATCH z4=(an2:hmm_source:antismash)<-[:SOURCE_DB]-(:hmm)-[:ANNOTATES]->(p1)
        WHERE an1.name ="Condensation"
            AND an2.name IN ["AMP-binding", "A-OX"]
            AND abs(e1.start - e2.start) < 10000
            AND e1.strand = e2.strand
    MATCH z5=(:hmm_source:amrfinder)<-[:SOURCE_DB]-(:hmm)-[:ANNOTATES]->(p2:protein)<-[e3:ENCODES]-(n1)
    WHERE abs(e1.start - e3.start) < 50000
            AND e1.strand = e3.strand
    RETURN z3, z4, z5
} in transactions of 1 rows
RETURN z1, z2, z3, z4, z5
```

This Neo4j Cypher query emulates the antiSMASH NRPS and halogenase BGC detection rules as copied below, with differing restrictions on distance between genes and the additional requirements of having a nearby antibiotic resistance gene and all the genes occurring on the same strand of DNA.

The following antiSMASH rules were copied from: https://github.com/antismash/antismash/blob/fa46d2c822b4bcca99a6c13bb1bf38a844bd49d7/antismash/detection/hmm_detection/cluster_rules/strict.txt

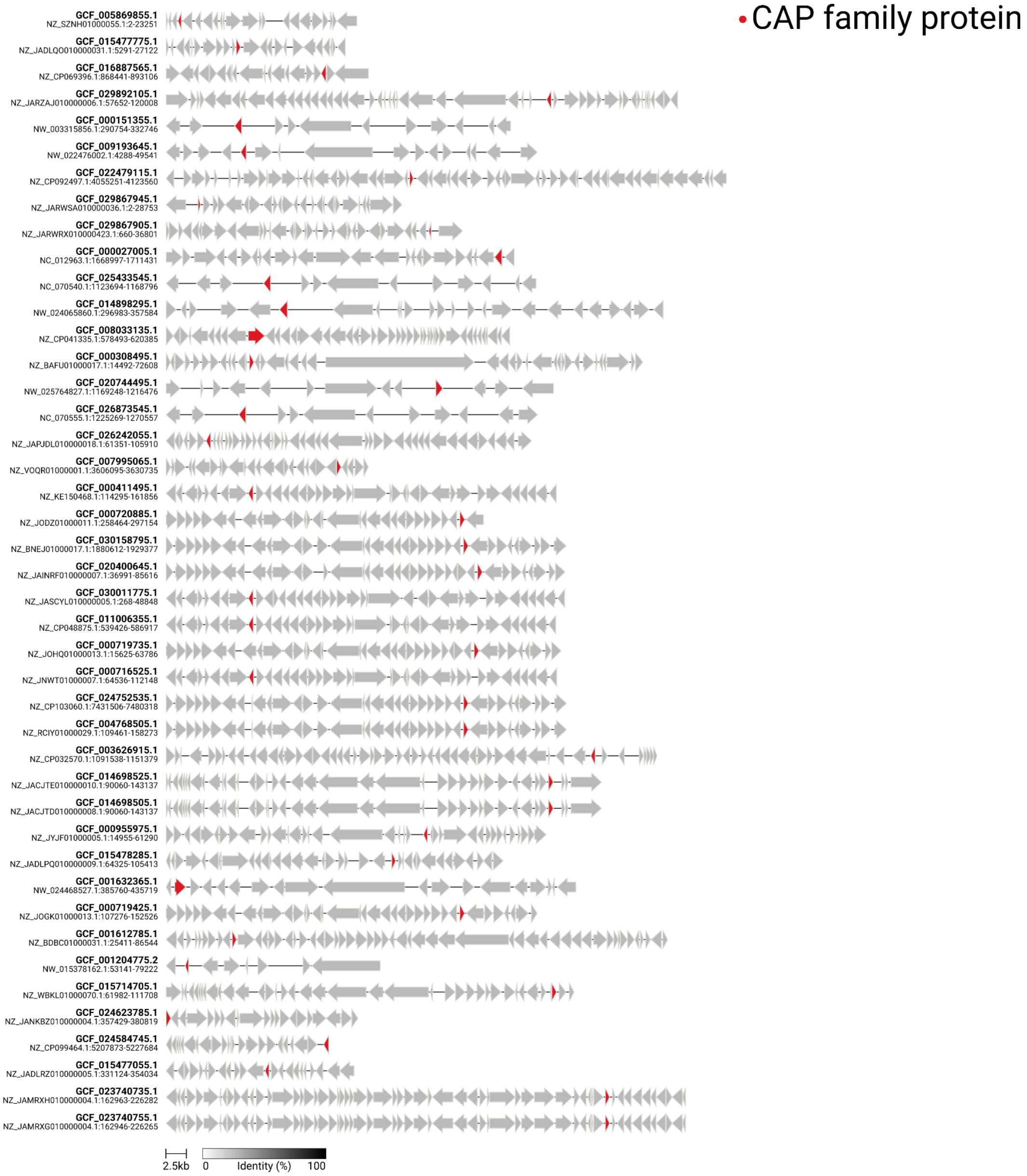
```
RULE halogenated
   CATEGORY other
   DESCRIPTION Halogenases are frequently involved in secondary metabolite biosynthesis
   SUPERIORS polyhalogenated-pyrrole
   CUTOFF 5
   NEIGHBOURHOOD 10
   CONDITIONS Trp_halogenase

RULE NRPS
   CATEGORY NRPS
   DESCRIPTION non-ribosomal peptide synthase
   CUTOFF 20
   NEIGHBOURHOOD 20
   CONDITIONS cds(Condensation and (AMP-binding or A-OX))
```

Supplementary Figure 19: Targeted drug discovery, halogenated NRP antibiotics



A screenshot of the Neo4j internet browser view of the results of the Cypher query in Supplementary Fig 18. The query successfully recovered halogenated NRP antibiotics from MIBiG (brown, labeled nodes).

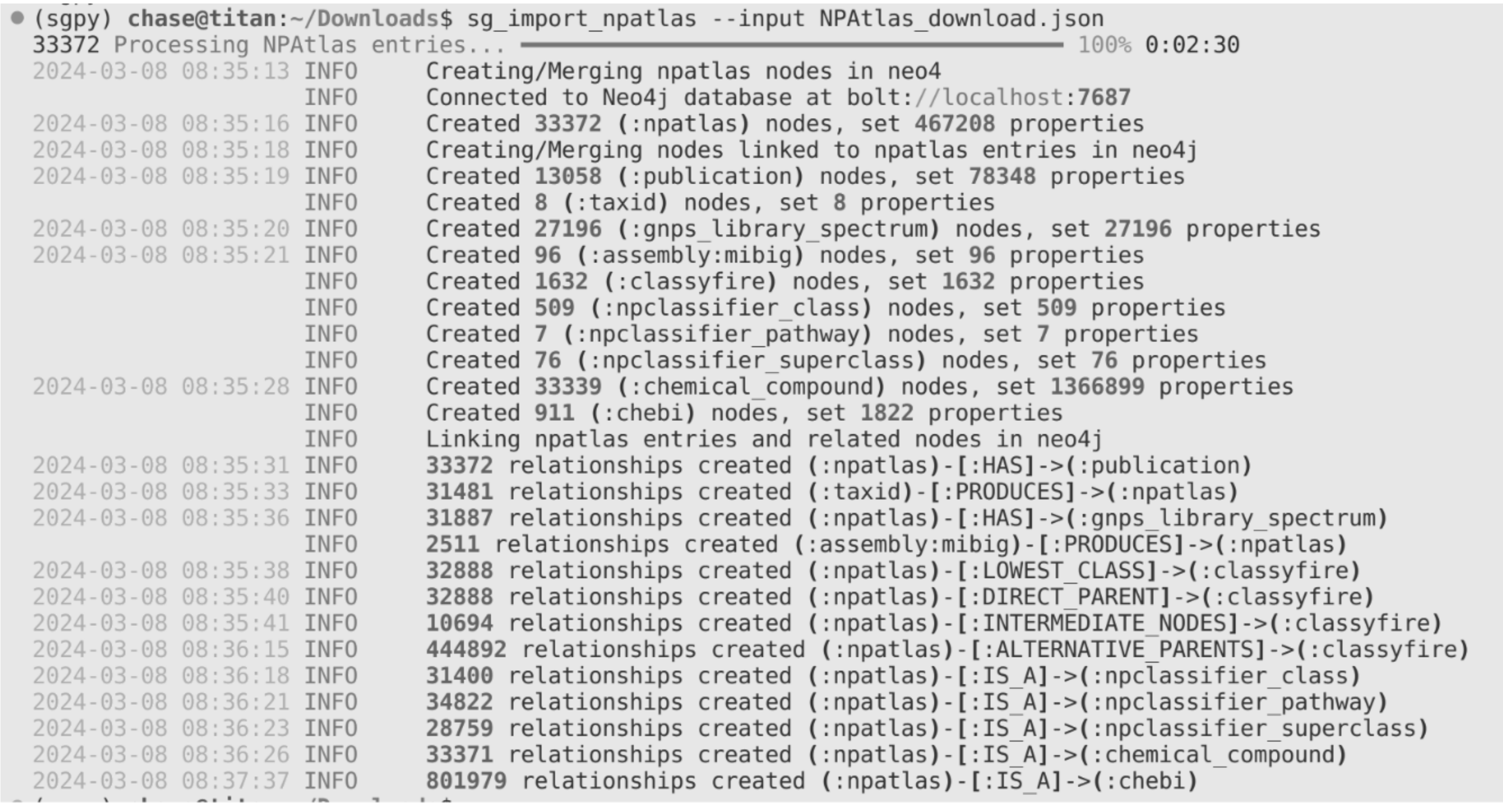
Supplementary Figure 20: SocialGene search for CAP superfamily protein containing BGCs



● CAP family protein
GCF_005869855.1
NZ_SZNH01000055.1:2-23251
GCF_015477775.1
NZ_JADLQO010000031.1:5291-27122
GCF_016887565.1
NZ_CP069396.1:868441-893106
GCF_029892105.1
NZ_JARZAJ010000006.1:57652-120008
GCF_000151355.1
NW_003315856.1:290754-332746
GCF_009193645.1
NW_022476002.1:4288-49541
GCF_022479115.1
NZ_CP092497.1:4055251-4123560
GCF_029867945.1
NZ_JARWSA010000036.1:2-28753
GCF_029867905.1
NZ_JARWRX010000423.1:660-36801
GCF_000027005.1
NC_012963.1:1668997-1711431
GCF_025433545.1
NC_070540.1:1123694-1168796
GCF_014898295.1
NW_024065860.1:296983-357584
GCF_008033135.1
NZ_CP041335.1:578493-620385
GCF_000308495.1
NZ_BAFU01000017.1:14492-72608
GCF_020744495.1
NW_025764827.1:1169248-1216476
GCF_026873545.1
NC_070555.1:1225269-1270557
GCF_026242055.1
NZ_JAPJDL010000018.1:61351-105910
GCF_007995065.1
NZ_VOQR01000001.1:3606095-3630735
GCF_000411495.1
NZ_KE150468.1:114295-161856
GCF_000720885.1
NZ_JODZ01000011.1:258464-297154
GCF_030158795.1
NZ_BNEJ01000017.1:1880612-1929377
GCF_020400645.1
NZ_JAINRF010000007.1:36991-85616
GCF_030011775.1
NZ_JASCYL010000005.1:268-48848
GCF_011006355.1
NZ_CP048875.1:539426-586917
GCF_000719735.1
NZ_JOHQ01000013.1:15625-63786
GCF_000716525.1
NZ_JNWT01000007.1:64536-112148
GCF_024752535.1
NZ_CP103060.1:7431506-7480318
GCF_004768505.1
NZ_RCIY01000029.1:109461-158273
GCF_003626915.1
NZ_CP032570.1:1091538-1151379
GCF_014698525.1
NZ_JACJTE010000010.1:90060-143137
GCF_014698505.1
NZ_JACJTD010000008.1:90060-143137
GCF_000955975.1
NZ_JYJF01000005.1:14955-61290
GCF_015478285.1
NZ_JADLPQ010000009.1:64325-105413
GCF_001632365.1
NW_024468527.1:385760-435719
GCF_000719425.1
NZ_JOGK01000013.1:107276-152526
GCF_001612785.1
NZ_BDBC01000031.1:25411-86544
GCF_001204775.2
NW_015378162.1:53141-79222
GCF_015714705.1
NZ_WBKL01000070.1:61982-111708
GCF_024623785.1
NZ_JANKBZ010000004.1:357429-380819
GCF_024584745.1
NZ_CP099464.1:5207873-5227684
GCF_015477055.1
NZ_JADLRZ010000005.1:331124-354034
GCF_023740735.1
NZ_JAMRXH010000004.1:162963-226282
GCF_023740755.1
NZ_JAMRXG010000004.1:162946-226265
2.5kb
0
Identity (%)
100

As proof of concept, >340,000 genomes (SocialGene RefSeq database) were searched for CAP protein containing BGCs (as annotated by antiSMASH 7). Utilizing SocialGene's Python library, the resulting putative BGC regions were converted to a clustermap.js plot and the putative CAP proteins highlighted in red.

Supplementary Figure 21: Screenshot showing the incorporation of NP Atlas into a SocialGene database



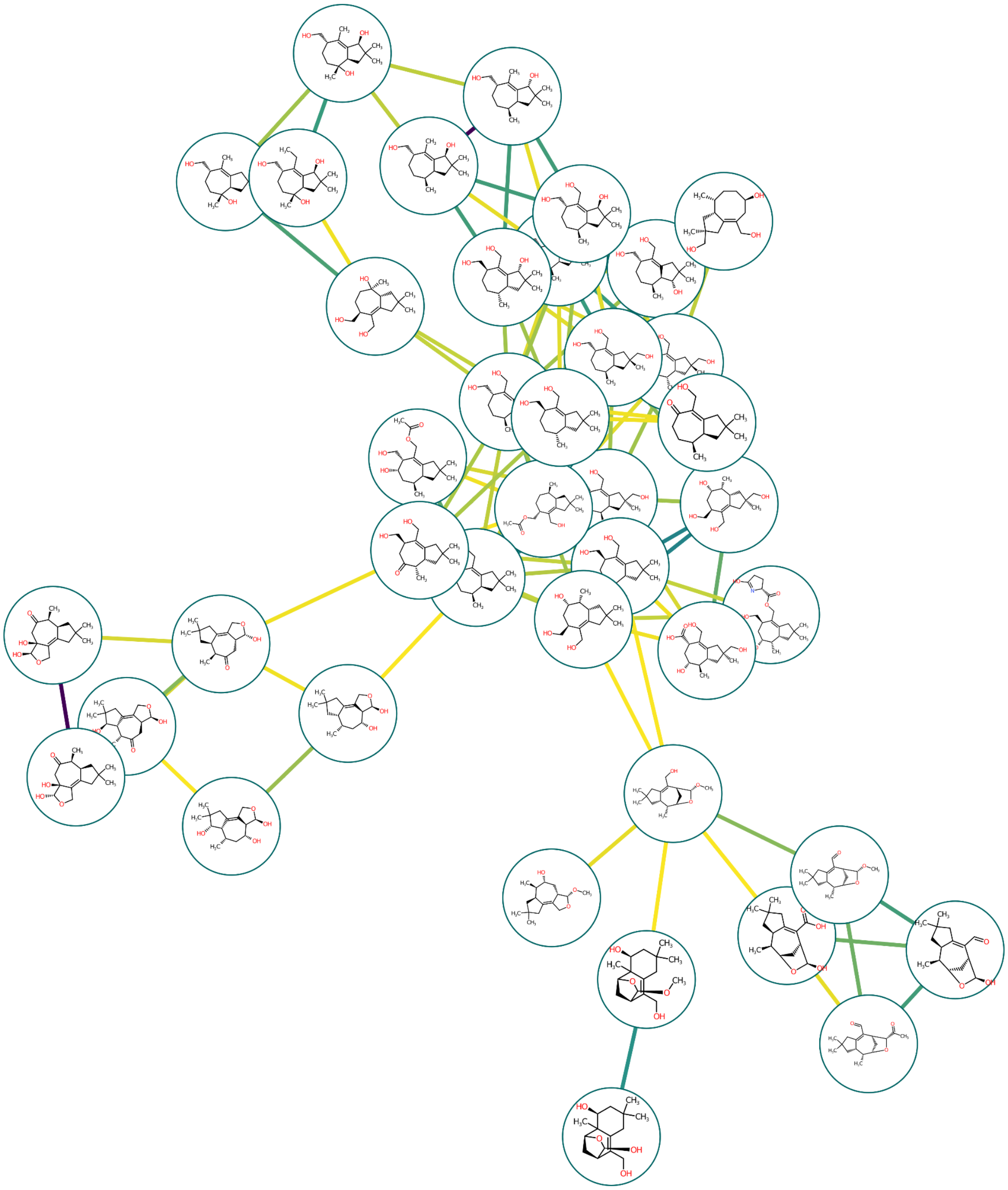
```
● (sgpy) chase@titan:~/Downloads$ sg_import_npatlas --input NPAtlas_download.json
  33372 Processing NPAtlas entries... ━━━━━━━━━━━━━━━━━━━━━━━━━━━━━━━━━━━━━━━━ 100% 0:02:30
  2024-03-08 08:35:13 INFO     Creating/Merging npatlas nodes in neo4
                      INFO     Connected to Neo4j database at bolt://localhost:7687
  2024-03-08 08:35:16 INFO     Created 33372 (:npatlas) nodes, set 467208 properties
  2024-03-08 08:35:18 INFO     Creating/Merging nodes linked to npatlas entries in neo4j
  2024-03-08 08:35:19 INFO     Created 13058 (:publication) nodes, set 78348 properties
                      INFO     Created 8 (:taxid) nodes, set 8 properties
  2024-03-08 08:35:20 INFO     Created 27196 (:gnps_library_spectrum) nodes, set 27196 properties
  2024-03-08 08:35:21 INFO     Created 96 (:assembly:mibig) nodes, set 96 properties
                      INFO     Created 1632 (:classyfire) nodes, set 1632 properties
                      INFO     Created 509 (:npclassifier_class) nodes, set 509 properties
                      INFO     Created 7 (:npclassifier_pathway) nodes, set 7 properties
                      INFO     Created 76 (:npclassifier_superclass) nodes, set 76 properties
  2024-03-08 08:35:28 INFO     Created 33339 (:chemical_compound) nodes, set 1366899 properties
                      INFO     Created 911 (:chebi) nodes, set 1822 properties
                      INFO     Linking npatlas entries and related nodes in neo4j
  2024-03-08 08:35:31 INFO     33372 relationships created (:npatlas)-[:HAS]->(:publication)
  2024-03-08 08:35:33 INFO     31481 relationships created (:taxid)-[:PRODUCES]->(:npatlas)
  2024-03-08 08:35:36 INFO     31887 relationships created (:npatlas)-[:HAS]->(:gnps_library_spectrum)
                      INFO     2511 relationships created (:assembly:mibig)-[:PRODUCES]->(:npatlas)
  2024-03-08 08:35:38 INFO     32888 relationships created (:npatlas)-[:LOWEST_CLASS]->(:classyfire)
  2024-03-08 08:35:40 INFO     32888 relationships created (:npatlas)-[:DIRECT_PARENT]->(:classyfire)
  2024-03-08 08:35:41 INFO     10694 relationships created (:npatlas)-[:INTERMEDIATE_NODES]->(:classyfire)
  2024-03-08 08:36:15 INFO     444892 relationships created (:npatlas)-[:ALTERNATIVE_PARENTS]->(:classyfire)
  2024-03-08 08:36:18 INFO     31400 relationships created (:npatlas)-[:IS_A]->(:npclassifier_class)
  2024-03-08 08:36:21 INFO     34822 relationships created (:npatlas)-[:IS_A]->(:npclassifier_pathway)
  2024-03-08 08:36:23 INFO     28759 relationships created (:npatlas)-[:IS_A]->(:npclassifier_superclass)
  2024-03-08 08:36:26 INFO     33371 relationships created (:npatlas)-[:IS_A]->(:chemical_compound)
  2024-03-08 08:37:37 INFO     801979 relationships created (:npatlas)-[:IS_A]->(:chebi)
```

SocialGene Python library's command line programs offer feedback and progress updates. Here NP Atlas is downloaded, parsed, and incorporated into a running SocialGene database.

Supplementary Figure 22: NP Atlas compounds linked by chemical similarity within a SocialGene database

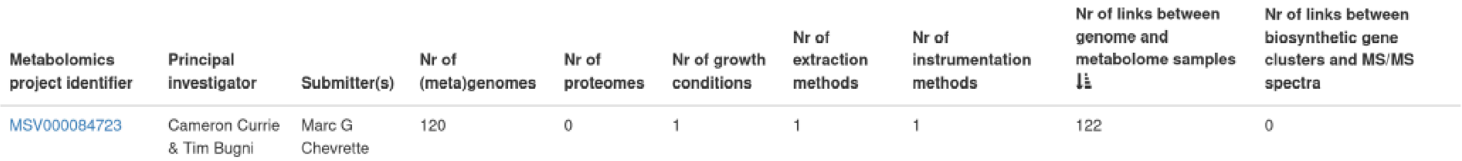
All NP Atlas compounds and all-vs-all chemical similarity relationships (Tanimoto) were imported into Cytoscape from a SocialGene database using the Neo4j Cytoscape plugin. As the number of genomes encompassing the taxonomic diversity of NP Atlas increases we expect more links and predictions can be made connecting BGCs to isolated compounds, and vice-versa. A zoom in is shown in Supplementary Figure 23.

Supplementary Figure 23: Screenshot showing Tanimoto-similarity links between chemical compounds in a SocialGene database

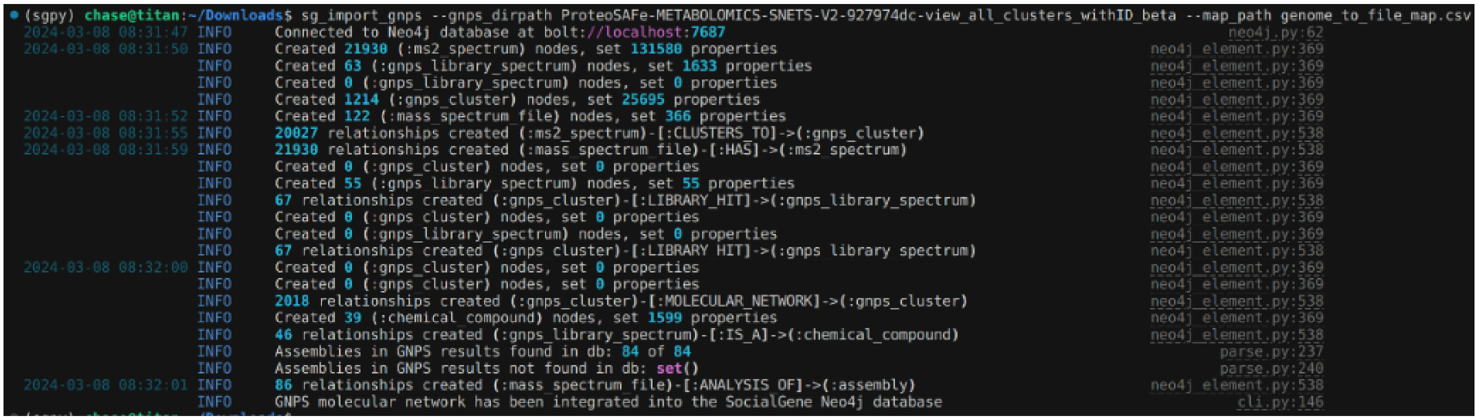


SocialGene has a command line function that calculates all-vs-all chemical similarity between all non-redundant chemical compounds in a running database. This allows users to create a coherent graph even when incorporating chemical structures from multiple databases and sources. The figure was generated using the Neo4j and chemviz2 plugins in Cytoscape and is a subset of Supplementary Figure 22.

Supplementary Figure 24: Screenshot showing the incorporation GNPS molecular networking results into a SocialGene database

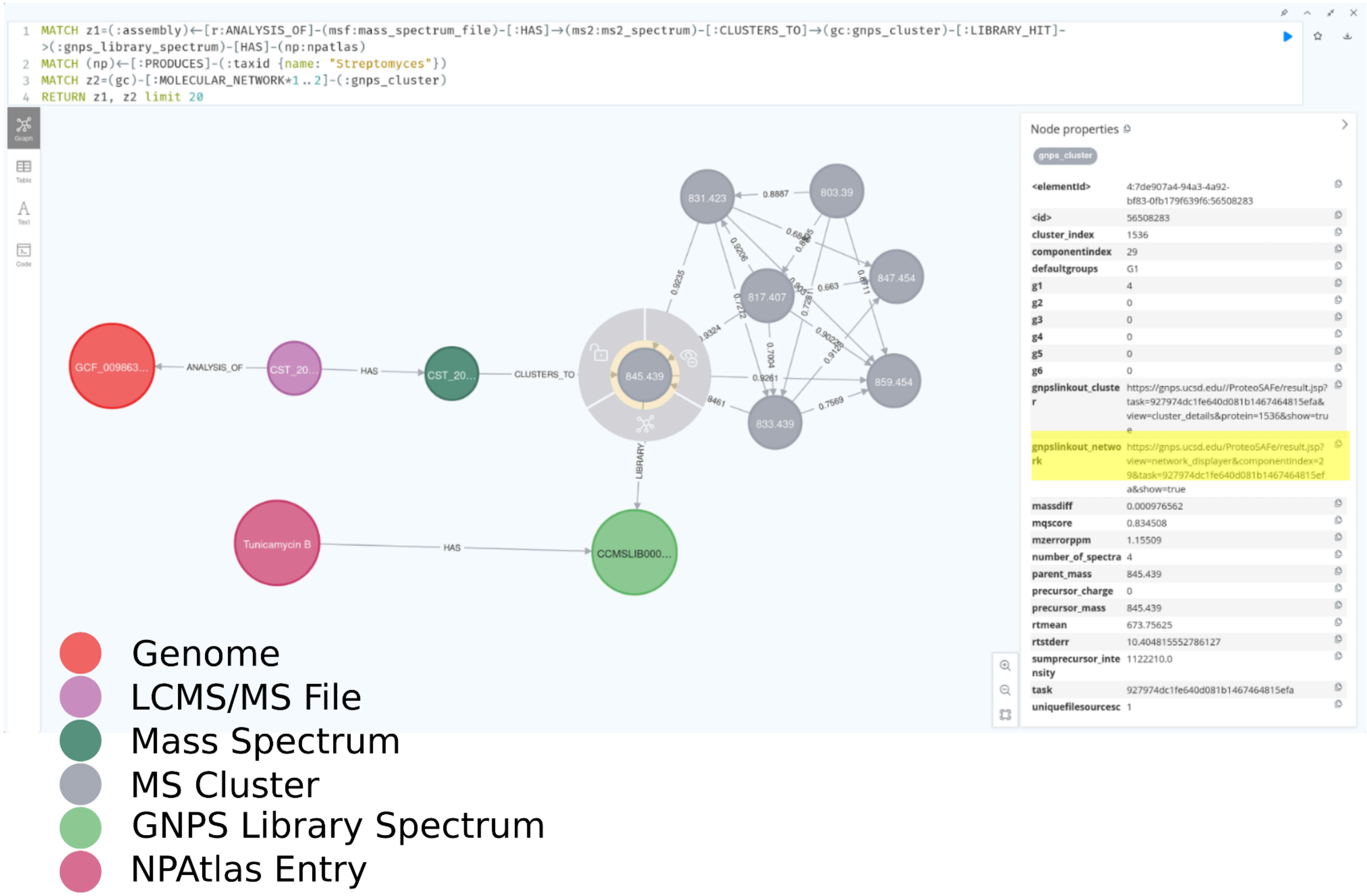


Metabolomics project identifier	Principal investigator	Submitter(s)	Nr of (meta)genomes	Nr of proteomes	Nr of growth conditions	Nr of extraction methods	Nr of instrumentation methods	Nr of links between genome and metabolome samples	Nr of links between biosynthetic gene clusters and MS/MS spectra
MSV000084723	Cameron Currie & Tim Bugni	Marc G Chevrette	120	0	1	1	1	122	0



```
● (sgpy) chase@titan:~/Downloads$ sg_import_gnps --gnps_dirpath ProteoSAFe-METABOLOMICS-SNETS-V2-927974dc-view_all_clusters_withID_beta --map_path genome_to_file_map.csv
  2024-03-08 08:31:47 INFO     Connected to Neo4j database at bolt://localhost:7687                                               neo4j.py:62
  2024-03-08 08:31:50 INFO     Created 21930 (:ms2_spectrum) nodes, set 131580 properties                                 neo4j_element.py:369
                      INFO     Created 63 (:gnps_library_spectrum) nodes, set 1633 properties                             neo4j_element.py:369
                      INFO     Created 0 (:gnps_library_spectrum) nodes, set 0 properties                                 neo4j_element.py:369
                      INFO     Created 1214 (:gnps_cluster) nodes, set 25695 properties                                   neo4j_element.py:369
  2024-03-08 08:31:52 INFO     Created 122 (:mass_spectrum_file) nodes, set 366 properties                                neo4j_element.py:369
  2024-03-08 08:31:55 INFO     20027 relationships created (:ms2_spectrum)-[:CLUSTERS_TO]->(:gnps_cluster)                neo4j_element.py:538
  2024-03-08 08:31:59 INFO     21930 relationships created (:mass_spectrum_file)-[:HAS]->(:ms2_spectrum)                  neo4j_element.py:538
                      INFO     Created 0 (:gnps_cluster) nodes, set 0 properties                                          neo4j_element.py:369
                      INFO     Created 55 (:gnps_library_spectrum) nodes, set 55 properties                               neo4j_element.py:369
                      INFO     67 relationships created (:gnps_cluster)-[:LIBRARY_HIT]->(:gnps_library_spectrum)          neo4j_element.py:538
                      INFO     Created 0 (:gnps_cluster) nodes, set 0 properties                                          neo4j_element.py:369
                      INFO     Created 0 (:gnps_library_spectrum) nodes, set 0 properties                                 neo4j_element.py:369
                      INFO     67 relationships created (:gnps_cluster)-[:LIBRARY_HIT]->(:gnps_library_spectrum)          neo4j_element.py:538
  2024-03-08 08:32:00 INFO     Created 0 (:gnps_cluster) nodes, set 0 properties                                          neo4j_element.py:369
                      INFO     Created 0 (:gnps_cluster) nodes, set 0 properties                                          neo4j_element.py:369
                      INFO     2018 relationships created (:gnps_cluster)-[:MOLECULAR_NETWORK]->(:gnps_cluster)           neo4j_element.py:538
                      INFO     Created 39 (:chemical_compound) nodes, set 1599 properties                                 neo4j_element.py:369
                      INFO     46 relationships created (:gnps_library_spectrum)-[:IS_A]->(:chemical_compound)            neo4j_element.py:538
                      INFO     Assemblies in GNPS results found in db: 84 of 84                                                 parse.py:237
                      INFO     Assemblies in GNPS results not found in db: set()                                                parse.py:240
  2024-03-08 08:32:01 INFO     86 relationships created (:mass_spectrum_file)-[:ANALYSIS_OF]->(:assembly)                 neo4j_element.py:538
                      INFO     GNPS molecular network has been integrated into the SocialGene Neo4j database                      cli.py:146
● (sgpy) chase@titan:~/Downloads$
```

Supplementary Figure 25: Connecting genomic and metabolomic data



```
MATCH z1=(:assembly)←[r:ANALYSIS_OF]-(msf:mass_spectrum_file)-[:HAS]→(ms2:ms2_spectrum)-[:CLUSTERS_TO]→(gc:gnps_cluster)-[:LIBRARY_HIT]-
>(:gnps_library_spectrum)-[HAS]-(np:npatlas)
MATCH (np)←[:PRODUCES]-(:taxid {name: "Streptomyces"})
MATCH z2=(gc)-[:MOLECULAR_NETWORK*1..2]-(:gnps_cluster)
RETURN z1, z2 limit 20
```

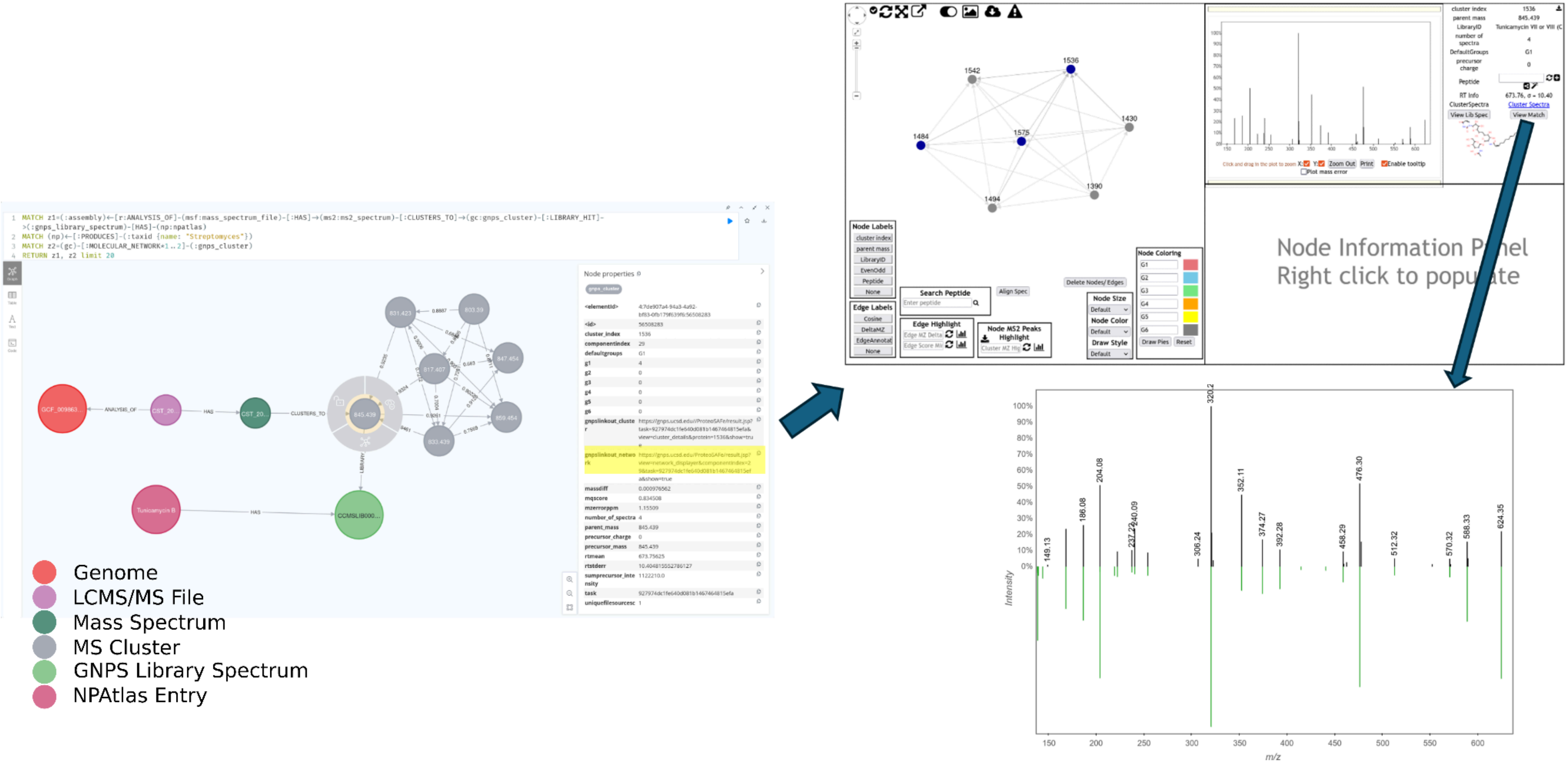
Node properties

gnps_cluster

<elementId>	4:7de907a4-94a3-4a92-bf83-0fb179f639f6:56508283
<id>	56508283
cluster_index	1536
componentindex	29
defaultgroups	G1
g1	4
g2	0
g3	0
g4	0
g5	0
g6	0
gnpslinkout_cluster	https://gnps.ucsd.edu//ProteoSAFe/result.jsp?task=927974dc1fe640d081b1467464815efa&view=cluster_details&protein=1536&show=true
gnpslinkout_network	https://gnps.ucsd.edu/ProteoSAFe/result.jsp?view=network_displayer&componentindex=29&task=927974dc1fe640d081b1467464815efa&show=true
massdiff	0.000976562
mqscore	0.834508
mzerrorppm	1.15509
number_of_spectra	4
parent_mass	845.439
precursor_charge	0
precursor_mass	845.439
rtmean	673.75625
rtstderr	10.404815552786127
sumprecursor_intensity	1122210.0
task	927974dc1fe640d081b1467464815efa
uniquefilesourcesc	1

A subset of the resulting graph imported in Supplementary Fig. 24. The query identifies genomes associated with an MS cluster, that has a GNPS library hit, that is found in NP Atlas, where the NP Atlas entry was isolated from a Streptomycete. Not shown are additional links out from the genome assembly (e.g. nucleotide sequences, proteins, pHMM annotations, etc.) and NP Atlas (e.g. chemical ontology, taxonomic source, etc.).

Supplementary Figure 26: SocialGene cross references MS clusters to GNPS website



```
MATCH z1=(:assembly)←[r:ANALYSIS_OF]-(msf:mass_spectrum_file)-[:HAS]→(ms2:ms2_spectrum)-[:CLUSTERS_TO]→(gc:gnps_cluster)-[:LIBRARY_HIT]-
>(:gnps_library_spectrum)-[HAS]-(np:npatlas)
MATCH (np)←[:PRODUCES]-(:taxid {name: "Streptomyces"})
MATCH z2=(gc)-[:MOLECULAR_NETWORK*1..2]-(:gnps_cluster)
RETURN z1, z2 limit 20
```

Node properties

gnps_cluster

<elementId>	4:7de907a4-94a3-4a92-bf83-0fb179f639f6:56508283
<id>	56508283
cluster_index	1536
componentindex	29
defaultgroups	G1
g1	4
g2	0
g3	0
g4	0
g5	0
g6	0
gnpslinkout_cluster	https://gnps.ucsd.edu//ProteoSAFe/result.jsp?task=927974dc1fe640d081b1467464815efa&view=cluster_details&protein=1536&show=true
gnpslinkout_network	https://gnps.ucsd.edu/ProteoSAFe/result.jsp?view=network_displayer&componentindex=29&task=927974dc1fe640d081b1467464815efa&show=true
massdiff	0.000976562
mqscore	0.834508
mzerrorppm	1.15509
number_of_spectra	4
parent_mass	845.439
precursor_charge	0
precursor_mass	845.439
rtmean	673.75625
rtstderr	10.404815552786127
sumprecursor_intensity	1122210.0
task	927974dc1fe640d081b1467464815efa
uniquefilesourcesc	1

cluster index	1536
parent mass	845.439
LibraryID	Tunicamycin VII or VIII (C
number of spectra	4
DefaultGroups	G1
precursor charge	0
Peptide	
RT Info	673.76, σ - 10.40
ClusterSpectra	Cluster Spectra

Here a mass spectrum cluster (gray node with additional ring), showing as a hit to a GNPS library spectrum, includes in its properties the url to view the cluster on the GNPS website where it was confirmed that the sample and library MS^2 spectra are nearly identical.

Supplementary Table 1: Types of antiSMASH-predicted BGCs containing a potential proteasome subunit, across >343,000 RefSeq genomes

BGC Type	Count
"[ectoine]"	257
"[NRPS-like]"	225
"[T3PKS]"	123
"[terpene]"	107
"[T1PKS]"	81
"[NRPS, T1PKS]"	74
"[NRPS]"	72
"[arylpolyene, resorcinol]"	69
"[NRPS-like, T1PKS]"	65
"[arylpolyene]"	57
"[NRP-metallophore, NRPS]"	38
"[fungal-RiPP-like]"	36
"[T1PKS, hglE-KS]"	34
"[betalactone]"	28
"[RiPP-like]"	27
"[acyl_amino_acids]"	19
"[acyl_amino_acids, hserlactone]"	17
"[NRPS, NRPS-like, T1PKS]"	16
"[T2PKS]"	15
"[T1PKS, terpene]"	15
"[hglE-KS]"	12
"[redox-cofactor]"	11
"[RRE-containing]"	11
"[lanthipeptide-class-v]"	11
"[RiPP-like, terpene]"	8
"[hserlactone]"	8
"[LAP]"	7
"[NAGGN]"	7
"[thiopeptide]"	7
"[NRPS-like, T1PKS, transAT-PKS-like]"	7
"[T1PKS, T2PKS]"	6
"[NAPAA]"	6
"[NI-siderophore]"	6

"[T3PKS, terpene]"	6
"[CDPS]"	5
"[cyanobactin]"	4
"[proteusin]"	4
"[NRP-metallophore, NRPS, acyl_amino_acids]"	4
"[T1PKS, betalactone, hglE-KS]"	4
"[phosphonate]"	4
"[phosphonate-like]"	4
"[NRPS-like, betalactone]"	3
"[arylpolyene, resorcinol, terpene]"	3
"[NRPS, hserlactone]"	3
"[other]"	3
"[NRPS, betalactone, transAT-PKS]"	3
"[lassopeptide]"	3
"[NRPS, NRPS-like]"	3
"[thioamitides, thiopeptide]"	2
"[indole]"	2
"[NRPS, NRPS-like, PKS-like, T1PKS, transAT-PKS-like]"	2
"[PKS-like]"	2
"[NRP-metallophore, NRPS, T1PKS]"	2
"[NRPS, PKS-like, T1PKS, terpene]"	2
"[2dos]"	2
"[NI-siderophore, NRPS]"	2
"[cyclic-lactone-autoinducer]"	2
"[NRPS, T1PKS, terpene]"	2
"[LAP, proteusin, thiopeptide]"	1
"[NRPS-like, T1PKS, hglE-KS, transAT-PKS-like]"	1
"[thioamitides]"	1
"[NRPS, NRPS-like, T1PKS, transAT-PKS-like]"	1
"[NRPS-like, RiPP-like, T1PKS, transAT-PKS]"	1
"[epipeptide]"	1
"[NRPS-like, terpene]"	1
"[NRPS, NRPS-like, transAT-PKS]"	1
"[NRPS, T1PKS, fungal-RiPP-like]"	1
"[T1PKS, fungal-RiPP-like]"	1
"[NRP-metallophore, NRPS, NRPS-like, T1PKS]"	1
"[arylpolyene, ectoine, resorcinol]"	1
"[NRPS, NRPS-like, T1PKS, T3PKS, terpene]"	1
"[isocyanide]"	1

"[NRPS, NRPS-like, T1PKS, betalactone, transAT-PKS-like]"	1
"[NRPS-like, transAT-PKS]"	1
"[lanthipeptide-class-iv]"	1
"[T1PKS, hglE-KS, oligosaccharide]"	1
"[NRPS, fungal-RiPP-like, terpene]"	1
"[isocyanide-nrp]"	1
"[mycosporine-like]"	1
"[fungal-RiPP]"	1
"[NAPAA, NRPS-like]"	1
"[NRPS, T1PKS, T3PKS, terpene]"	1
"[LAP, NRPS, T1PKS, thioamitides, thiopeptide]"	1
"[LAP, thiopeptide]"	1
"[methanobactin]"	1
"[linaridin]"	1
"[NRPS, NRPS-like, T1PKS, phenazine]"	1
"[PKS-like, T1PKS, terpene]"	1
"[ranthipeptide]"	1
"[T1PKS, T2PKS, transAT-PKS]"	1
"[NRPS, fungal-RiPP-like]"	1
"[transAT-PKS-like]"	1
"[fungal-RiPP, fungal-RiPP-like]"	1
"[NAGGN, T1PKS]"	1
"[T1PKS, T3PKS]"	1

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