Computational Genomics

Complete Genomes

Semi-Automated Feature Identification And Annotation

Evolutionary Analysis

Organism Phylogeny

Reconstructing Gene Histories

Horizontal Gene Transfer Studies

Chromosomal Cluster Phylogeny

Comparative Analysis

Subsystems Analysis

Gene Function Clarification

Encoding Pathway Variants

Subsystem Phylogenetics

Model Development

Reaction Set Determination

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Reaction Database

Encoding Reaction Variants

S Matrix Generation

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Transcription Regulation Signaling

Systems Analysis

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Phenotype Prediction

Constraints Observations

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Reaction Rates

Kinetics Based Models

Allosteric Regulation

Evolution of Kinetics

Personal Tools

Community Access

P2P Micropublishing

Web Services

Open Grids

[redacted]

Subsystems and in The SEED

Subsystem: NAD and NADP cofactor biosynthesis global

Functional Roles

Column	Abbrev	Functional Role
1	TDO	Tryptophan 2,3-dioxygenase (EC 1.13.11.11)
2	IDO	Indoleamine 2,3-dioxygenase (EC 1.13.11.42)
3	KFA_e	Kynurenine formamidase (EC 3.5.1.9)
4	KFA_b	Kynurenine formamidase, bacterial (EC 3.5.1.9)
5	KMO	Kynurenine 3-monooxygenase (EC 1.14.13.9)
6	KYN	Kynureninase (EC 3.7.1.3)
7	HAD	3-hydroxyanthranilate 3,4-dioxygenase (EC 1.13.11.6)
8	ASPOX	L-aspartate oxidase (EC 1.4.3.16)
9	ASPDH	Aspartate dehydrogenase [same functional role as] (EC 1.4.3.16)
10	QSYN	Quinolinate synthetase (EC 4.1.99.-)
11	QAPRT	Quinolinate phosphoribosyltransferase [decarboxylating] (EC 2.4.2.19)
12	NAMNAT	Nicotinate-nucleotide adenylyltransferase (EC 2.7.7.18)
13	NMNAT	Nicotinamide-nucleotide adenylyltransferase (EC 2.7.7.1)
14	NADS	NAD synthetase (EC 6.3.1.5)
15	GAT	Glutamine amidotransferase chain of NAD synthetase
16	NADK	NAD kinase (EC 2.7.1.23)

Subsets of Roles

Subset	Includes These Roles
*ASPOX	8,9
*KFA	3,4
*PNAT	12,13
*RNK	21,22
*TDO	1,2
Bacterial_type	8,9,10,11,12,13,14,15,16,17,18,19,20,21
Eukaryotic_type	1,2,3,4,5,6,7,11,12,13,14,15,16,17,18,19,22

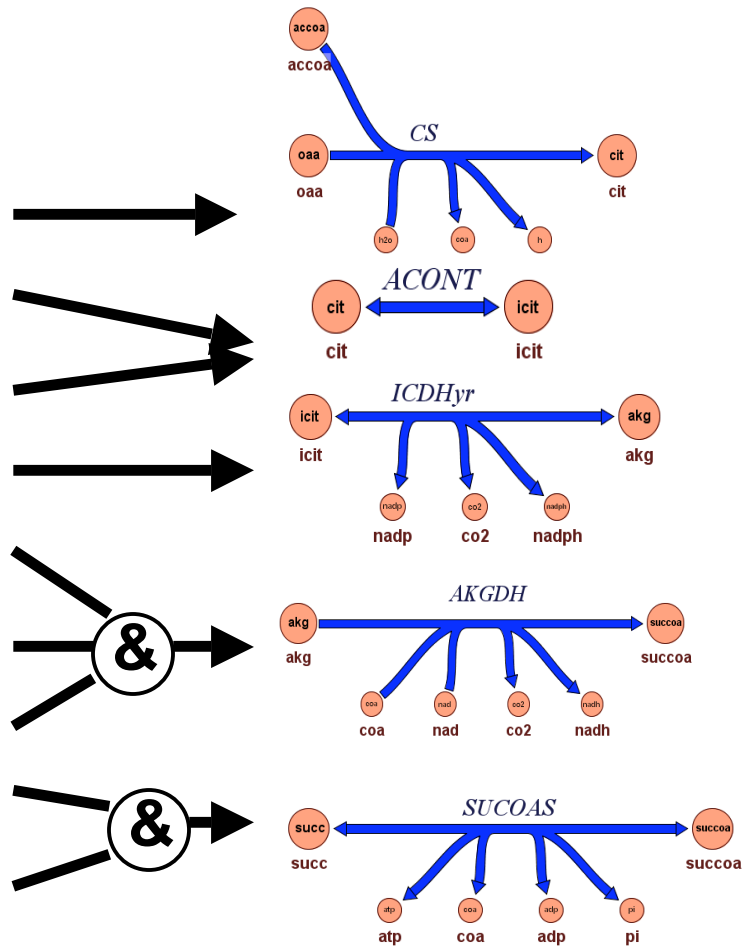
Genome ID	Organism	Variant Code	*TDO	*KFA	KMO	KYN	HAD	QAPRT	*PNAT	NADS	GAT	NADK	NAM	NAPRT	NMPRT	*RNK
28450.1	Burkholderia pseudomallei K96243 [B]	1	5488-1	5486-4		5487		5411	3781-12	3924 6430	3924	3300	1439	4058 5625		
227377.1	Coxiella burnetii RSA 493 [B]	1						94	531-12	821	821	1232		983		
165597.1	Crocosphaera watsonii WH 8501 [B]	4						4296	600-12			2279 6136	5122	601		
985.1	Cytophaga hutchinsonii [B]	8	2355-1		839	840	841		262-12			867			1073	2710-22
211586.1	Shewanella oneidensis MR-1 [B]	4				4007			1087-12	1842		1411			1809	

Functional Roles and Reaction Sets

Reactions in the context of the pathway should be associated with each functional gene annotation

Functional Roles

Col	Abr	Functional Role
1	gltA	Citrate synthase (EC 2.3.3.1)
2	acn B	Aconitate hydratase 2 (EC 4.2.1.3)
3	acn A	Aconitate hydratase (EC 4.2.1.3)
4	icd	Isocitrate dehydrogenase (EC 1.1.1.42)
5	suc A	2-oxoglutarate dehydrogenase E1 component (EC 1.2.4.2)
6	suc B	2-oxoglutarate dehydrogenase E2 component (EC 2.3.1.61)
7	lpdA	Dihydrolipoamide dehydrogenase (EC 1.8.1.4)
8	suc D	Succinyl-CoA synthetase alpha chain (EC 6.2.1.5)
9	suc C	Succinyl-CoA synthetase beta chain (EC 6.2.1.5)



Subsystems to Reaction Networks

The reactions that are associated with an organism are combined to form a network based on the subsystems

Genome ID	Organism	Variant Code	*TDO	*KFA	KMO	KYN	HAD	QAPRT	*PNAT	NADS	GAT	NADK	NAM	NAPRT	NMPRT	*RNK
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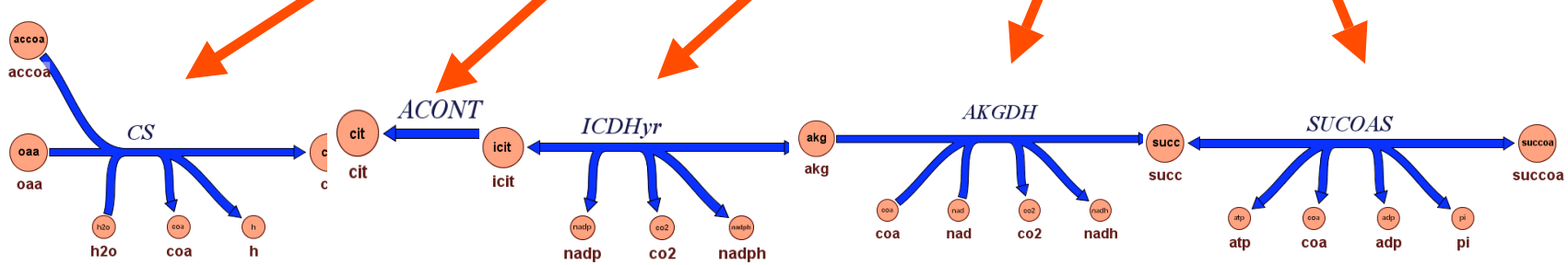
211586.1	Shewanella oneidensis MR-1 [B]	4				4007			1087-12	1342		1411			1809	



~200 Subsystems Currently Under Development

ABC transporter alkylphosphonate (TC 3.A.1.9.1)
ABC transporter arabinose (TC 3.A.1.2.2)
ABC transporter branched-chain amino acid (TC 3.A.1.4.1)
ABC transporter dipeptide (TC 3.A.1.5.2)
ABC transporter ferric enterobactin (TC 3.A.1.14.2)
ABC transporter ferrichrome (TC 3.A.1.14.3)
ABC transporter galactose (TC 3.A.1.2.3)
ABC transporter glutamate aspartate (TC 3.A.1.3.4)
ABC transporter glutamine (TC 3.A.1.3.2)
ABC transporter glycerol (TC 3.A.1.1.3)
ABC transporter heme (TC3.A.1.107.1)
ABC transporter histidine lysine arginine ornithine (TC 3.A.1.3.1)
ABC transporter iron(III) dicitrate (TC 3.A.1.14.1)
ABC transporter L-proline glycine betaine (TC 3.A.1.12.1)
ABC transporter macrolide
ABC transporter maltose
ABC transporter molybdenum (TC 3.A.1.8.1)
ABC transporter nickel (TC 3.A.1.5.3)
ABC transporter oligopeptide (TC 3.A.1.5.1)
ABC transporter peptide (TC 3.A.1.5.5)
ABC transporter phosphate (TC 3.A.1.7.1)
ABC transporter polyamine putrescine spermidine (TC 3.A.1.11.1)
ABC transporter putrescine (TC 3.A.1.11.2)
ABC transporter ribose (TC 3.A.1.2.1)
Acetogenesis_from_Pyruvate
Adhesion_to_eukaryotic_cell
Aerobic_respiratory_dehydrogenases
Alanine_Biosynthesis
Allantoin_degradation
Ammonia_assimilation
Anaerobic_respiratory_dehydrogenases
Anaerobic_respiratory_reductases
Arginine_Biosynthesis
Arginine_degradation
Asp-Glu-tRNA(Asn-Gln)_transamidation
Bacterial_Cell_Division
Betaine_biosynthesis
Bilin_Biosynthesis
Biotin_biosynthesis
Calvin-Benson_cycle
carnitine_metabolism
Carotenoids
Chaperones
Chlorophyll_Biosynthesis
Chorismate_Synthesis
CMP-N-acetylneuraminate_Biosynthesis
Coenzyme_A_Biosynthesis
Cyanobacterial_Circadian_Clock
Cyanobacterial_CO2_uptake
Cyanophycin_metabolism
cysteine_biosynthesis
Cytochrome_B6-F_complex
Cytolethal_distending_toxin_of_Campylobacter_jejuni
D-arabinose_degradation
D-galactarate_degradation
D-galacturonate_degradation
D-glucarate_degradation
De_Novo_Purine_Biosynthesis
De_Novo_Pyrimidine_Synthesis
Denitrification
DNA-replication
DNA_Repair_Base_Excision
dTDP-rhamnose_synthesis
Embden-Meyerhof_and_Gluconeogenesis
Enterobactin_biosynthesis
Entner-Doudoroff_Pathway
F0F1-type_ATP_synthase
Fatty_Acid_Biosynthesis_FASII
fatty_acid_metabolism
fatty_acid_oxidation_pathway
Fe-S_cluster_assembly
Flagellum
FMN_and_FAD_biosynthesis
Folate_biosynthesis
Formate_hydrogenase
Fructose_and_Mannose_metabolism
Fumarate_reductase
Galactitol_degradation
Galactose_degradation
General_secretory_pathway_(Sec-SRP)_complex_(TC_3.A.5.1.1)
Glutamate_biosynthesis
Glutathione_Redox_Metabolism
Glycerol_Metabolism
Glycerolipid_metabolism
Glycine_synthesis
glyoxylate_degradation
Glyoxylate_Synthesis
GroEL_GroES
Histidine_Biosynthesis
Histidine_Degradation
HMG_CoA_Synthesis
Inorganic_Sulfur_Assimilation
Inositol_catabolism_by_VV
Iron_Aquisition
Isoprenoid_Biosynthesis
Ketogluconate_metabolism
L-ascorbate_degradation
Lactose_degradation
Leucine_Degradation_and_HMG-CoA_Metabolism
Leucine_synthesis
Lysine_Biosynthesis_DAP_Pathway
Mannose-sensitive_hemagglutinin_type_4_pilus
Mannose_and_fructose__metabolism
mannose_and_GDP-mannose_metabolism
Menaquinone_and_Phylloquinone_Biosynthesis
Methanogenesis
Methionine_Biosynthesis
Methionine_Metabolism
Methylcitrate_cycle
N-Acetyl-D-Glucosamine_Utilization
N-linked_Glycosylation_in_Bacteria
NAD_and_NADP_cofactor_biosynthesis_global
NADH-quinone_oxidoreductase_(Complex__I)
NADH-ubiquinone_oxidoreductase_(Complex_I)
Nitrate,nitrite,_nitrous_oxide_reductases
Nitrate_and_Nitrite_Reduction
Nitrate_Assimilation
Nitrite_Reduction
Nitrosative_stress
P-type_ATPase_transporter_potassium_(TC_3.A.3.7.1)
Pentose_phosphate_pathway_(SG)
Peptidoglycan_Biosynthesis
Phenylalanine_synthesis
Photosystem_I
Photosystem_II
Phycobilisome
Plastoquinone_Biosynthesis
Polyamine_Metabolism
Porphyrin,_Heme,_and_Siroheme_Biosynthesis
ppGpp_biosynthesis
Proline_Synthesis
Propionate_Catabolism_via_2-Methylcitrate_Cycle
Proteasome_archaeal
Proteasome_eukaryotic
Pterin_biosynthesis
purine_conversions
purine_conversions_2
Putrescine_and_4-aminobutyrate_degradation
pyrimidine_conversions
Pyruvate,_PEP_and_Acetyl-CoA_(anaplerotic_reactions)
Pyruvate_Alanine_Serine_Interconversions
Queuosine
Resistance_to_fluoroquinolones
Riboflavin_metabolism
Ribonucleotide_reduction
Ribosome_biogenesis_bacterial
Ribosome_LSU_bacterial
Ribosome_LSU_eukaryotic_and_archaeal
Ribosome_SSU_bacterial
Ribosome_SSU_chloroplast
Ribosome_SSU_eukaryotic_and_archaeal
RNA_polymerase_archaeal
RNA_polymerase_archaeal_initiation_factors
RNA_polymerase_bacterial
RNA_polymerase_chloroplast
RNA_polymerase_I
RNA_polymerase_II
RNA_polymerase_II_initiation_factors
RNA_polymerase_III
Serine_Biosynthesis
Soluble_cytochromes_and_functionally_related_electron_carriers
Succinate__dehydrogenase
Sucrose_Metabolism
Sulfate_assimilation
Sulfur_Metabolism
superpathway_of_fucose_and_rhamnose_degradation
superpathway_of_glutamate,_aspartate,_asparagine_biosynthisis
superpathway_of_hexitol_degradation
superpathway_of_ribose_and_deoxyribose_phosphate_metabolism
TCA_Cycle
Terminal_cytochrome__oxidases
Terminal_cytochrome_C_oxidases
Thermotoga_Alanine_Biosynthesis
Thiamin_biosynthesis
Threonine_synthesis
Threonine_to_Isoleucine
Tocopherol_Biosynthesis
Transcription_factors_archaeal
Transcription_factors_bacterial
Translation_elongation_factors_eukaryotic_and_archaeal
Translation_factors_bacterial
Translation_initiation_factors_eukaryotic_and_archaeal
Transport_of_Nickel_and_Cobalt
Trehalose_biosynthesis
Tricarballylate_Utilization
tRNA_aminoacylation
tRNA_processing
tRNA_splicing
Trp_Synthesis
Type_II_secretion_system
Type_III_secretion_system
Type_IV_secretion_system
Tyrosine_synthesis
Ubiquinone_Biosynthesis
Ubiquinone_Menaquinone-cytochrome_c_reductase_complexes
UDP-N-acetylmuramate_from_Fructose-6-phosphate_Biosynthesis
Urea_decomposition
V-Type_ATP_synthaase

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Genome-scale reconstruction of the metabolic network in Staphylococcus aureus N315: an initial draft to the two-dimensional annotation

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Abstract

Background: Several strains of bacteria have sequenced and annotated genomes, which have been used in conjunction with biochemical and physiological data to reconstruct genome-scale metabolic networks. Such reconstruction amounts to a two-dimensional annotation of the genome. These networks have been analyzed with a constraint-based formalism and a variety of biologically meaningful results have emerged. *Staphylococcus aureus* is a pathogenic bacterium that has evolved resistance to many antibiotics, representing a significant health care concern. We present the first manually curated elementally and charge balanced genome-scale reconstruction and model of *S. aureus*' metabolic networks and compute some of its properties.

Results: We reconstructed a genome-scale metabolic network of *S. aureus* strain N315. This reconstruction, termed iSB619, consists of 619 genes that catalyze 640 metabolic reactions. For 91% of the reactions, open reading frames are explicitly linked to proteins and to the reaction. All but three of the metabolic reactions are both charge and elementally balanced. The reaction list is the most complete to date for this pathogen. When the capabilities of the reconstructed network were analyzed in the context of maximal growth, we formed hypotheses regarding growth requirements, the efficiency of growth on different carbon sources, and potential drug targets. These hypotheses can be tested experimentally and the data gathered can be used to improve subsequent versions of the reconstruction.

Conclusion: iSB619 represents comprehensive biochemically and genetically structured information about the metabolism of S. aureus to date. The reconstructed metabolic network can be used to predict cellular phenotypes and thus advance our understanding of a troublesome pathogen.

FB Model of Staphylococcus aureus

- Scott Becker and Bernard Palsson @ UCSD
- *i*SB619
  - 619 genes
  - 537 proteins
  - 640 metabolic reactions
  - 581 reactions linked to genes
  - 571 metabolites
  - 84 exchange fluxes

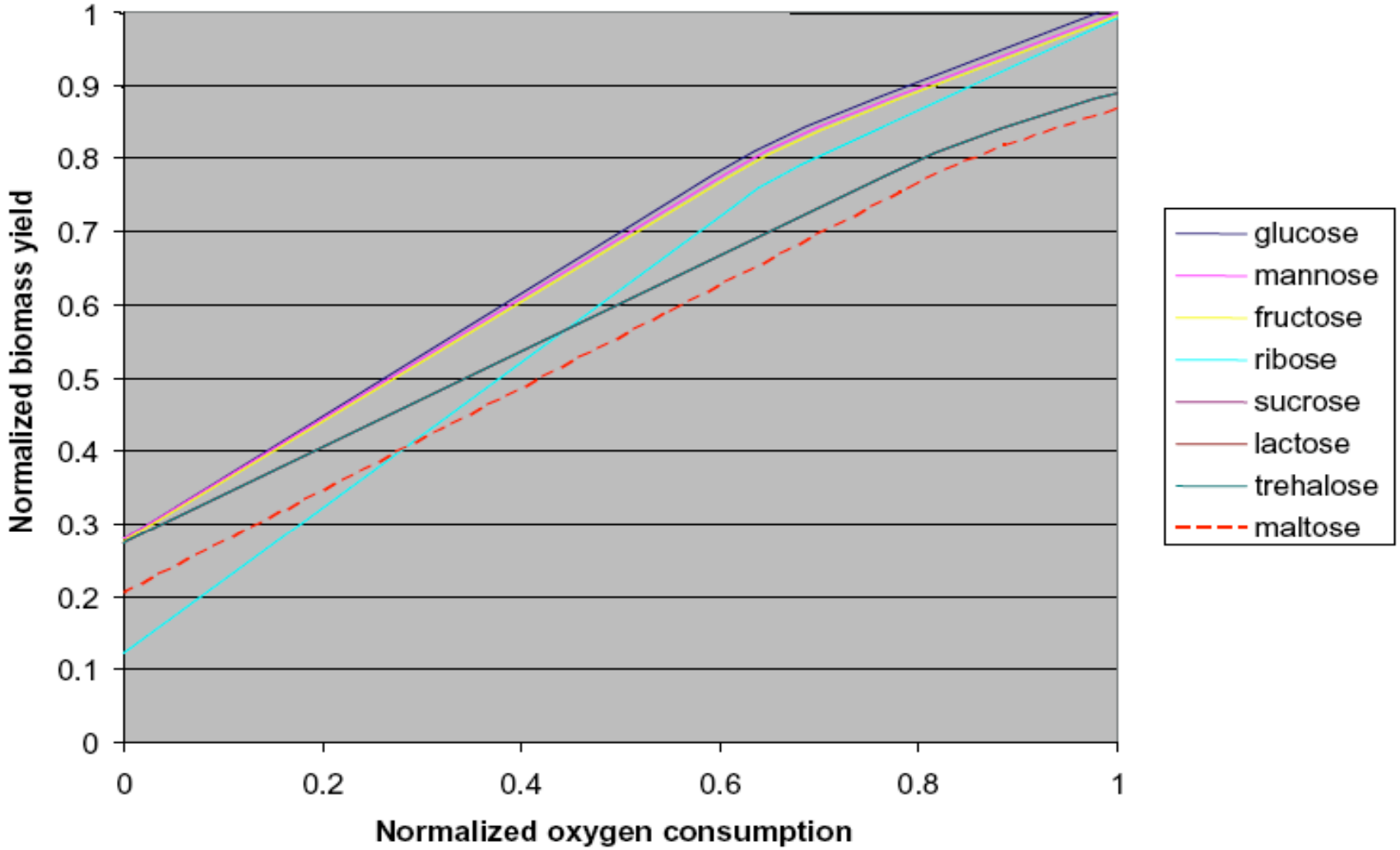

Figure 2
Relative growth efficiency with different carbon sources. The in silico growth of *i*SB619 varies depending on which carbon source is provided and the amount of oxygen present. The predicted efficiency of carbon incorporation into biomass is shown here as a function on the oxygen consumption. Growth rate is normalized relative to the number of carbon atoms per molecule. Oxygen consumption is normalized relative to optimal oxygen consumption for each carbon source. Trehalose, lactose, and sucrose all overlap (the trehalose line indicates all three). The legend is presented in the same order as the carbon sources appear in the figure, top to bottom.

Table 3: Essential enzymes and potential chemical inhibitors

Enzyme name	Potential Inhibitor	Prior testing?	Reference
acetyl-CoA carboxylase	pseudopeptide pyrrolidine dione antibiotics	SA, B	[45]
4-amino-4-deoxychorismate synthase	(6s)-6-fluoroshikimate	B	[46]
Adenosylmethionine decarboxylase	CGP 40215A, AdoMao	B	[47,48]
asparagine synthase (glutamine-hydrolysing)	mucochloric and mucobromic acids, L-cysteine sulfinic acid	B	[49,50]
dihydrofolate reductase	methylpteridines	B	[51]
dihydropteroate synthase	Sulfone and sulfanilamide sulfa drugs	B	[52,53]
3-dehydroquinate synthase	carbocyclic inhibitors	B	[54]
FMN adenylyltransferase (FAD synthase)	Riboflavin 5'-pyrophosphate	F	[55]
glycerol-3-phosphate dehydrogenase (NADP)	5-n-alk(en)ylresorcinols	NF	[56]
glutamine synthetase	L-methionine sulfoximine, aminomethylene-bisphosphonic acid derivatives	NF	[57,58]
glutamyl-tRNA reductase	see table 1 in paper	NF	[59]
GTP cyclohydrolase I	Diamino-6-hydroxypyrimidine, pterins	NF	[60,61]
Hydroxymethylglutaryl CoA reductase (ir)	statins	NF	[62,63]
Hydroxymethylglutaryl CoA synthase (ir)	beta-lactone, 3-Hydroxy-3-methylglutaryldithio-coenzyme A	NF	[64,65]
isopentenyl-diphosphate D-isomerase	NE21650	NF	[66]
methionine adenosyltransferase	adduncts 14 and 16	B	[67]
Phosphatidate phosphatase	Propranolol	NF	[68]
phosphoribosylpyrophosphate synthetase	MRPP, ARPP	NF	[69]
riboflavin synthase	9-D-ribitylamino-1,3,7,9-tetrahydro-2,6,8-purinetriones	B	[70]
spermidine synthase	adenosylspermidine, dicyclohexylamine	SA, B	[71,72]
thiamine transport via ABC system	azidobenzoyl derivatives of thiamin, methylene blue	F	[73,74]
thioredoxin reductase	Arsenicals, Aurothioglucose	NF	[75,76]
UDP-N-acetylglucosamine 4-epimerase	uridine analogs	NF	[77]
UDP-N-acetylenolpyruvoylglucosamine reductase	4-thiazolidinones	B	[78]

A reasonable number of enzymes that are computationally predicted to be essential for the growth of *S. aureus* have inhibitors. These molecules are potential drugs against this organism. The prior testing column uses abbreviations to indicate if we located evidence that the listed compounds had been tested in *S. aureus* (SA), other bacteria (B), fungi (F), or if no evidence was located (NF). The interested reader should consult the relevant references for full details regarding these potential inhibitors.