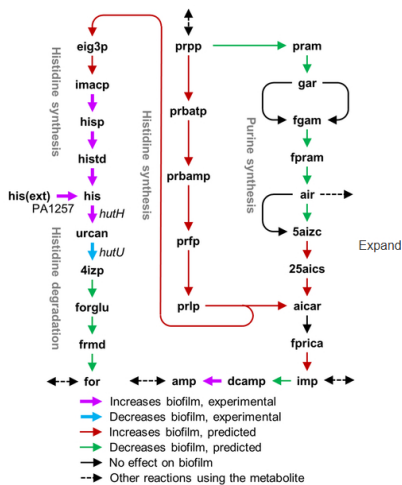


[< Back to Article](#)**Fig 1.**

Alteration of biofilm formation by different reaction inhibitions in the histidine and purine synthesis pathways.

Reactions indicated with magenta and cyan arrows were experimentally identified by Musken et al. [22]. We predicted reactions indicated with red and green arrows. Abbreviations: aicar, 5-phosphoribosyl-4-carbamoyl-5-aminoimidazole; prpp, 5-phosphoribosyl diphosphate; amp, adenylate. See [S1 Supporting Information](#) for the definition of the remaining of the abbreviations.

[More »](#)**Table 1.**

Putative target reactions against biofilm that also would decrease antimicrobial tolerance or attenuate virulence.

[More »](#)

Reaction name	Reaction	Genes	Identification method ^a
Reduced antimicrobial tolerance			
N-acetyl-g-glutamyl-phosphate reductase	acglsia + nadp + pi <=> acglp + h + nadph	argC	P
Fumismidylglutamate	forglu + h2o => fmd + glu-L	hutG or PA3175	P
Attenuated virulence			
1,2-bisacyl-sn-glycerol 3-phosphate synthase	1.02 2hdaACP + gly3h = 0.36 hdaACP + 0.06 ocaACP + 0.96 (glaY or pldA or pldB) and (glaF or oiaA)	glaY or pldA or pldB and (glaF or oiaA)	E
Isochorismate Synthase	chor => khor	pchA	E
Oxidative 5-phosphate decarboxylase	h + oadp => co2 + ump	pyrF	E
Protoporphyrinogen oxidase	1.5 o2 + ppgH => 3 h2o + ppgH	hemY or hemK	E
Arginine N-acetyltransferase	arg-L + succoa => succoa + coa + h	anf and argD	P
1-hydroxyphenazine synthase	h + nadh + o2 + pda => 1hph + co2 + h2o + nad	phtS	P
Phenazine-1-carboxylic acid synthase, step 1	chor + glu-L => e4dc + glu-L	phtE1 or phtE2	P
Phenazine-1-carboxylic acid synthase, step 2	e4dc + h2o => dhha + h + pyr	phtD1 or phtD2	P
Pharmoxyltransferase chain A	3hdaACP + coa => 3hdcooa + ACP	nra	P
Isochorismate-pyruvate lyase	ichor => sal + pyr	pchB	P
Pyochelin synthase pchOG	salamp + cysamp => hphthiazoline + 2 amp + h2o + h	pchG and pchD	P

^a E, reaction associated with an experimentally determined mutant; P, predicted.

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Table 2.

Reactions with predicted median flux ratio change of at least 2-fold in biofilm cultures compared to stationary cultures.

[More »](#)

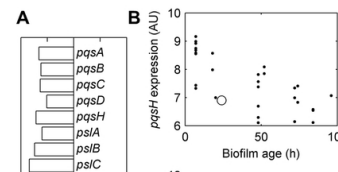
Reaction name	Reaction	Genes	GE ratio ^a	Flux ratio ^b
Down-regulated				
HMG synthesis ^c	3oxhACP + anrh + h => ACP + co2 + h2o + hmg	pqsABCD	0.40	0.47
Probable FAD-dependent monooxygenase (PQS synthesis) ^c	fadH2 + hmg + o2 => fad + h2o + pqs	pqsH	0.99	0.47
Acy ACP:matrony ACP C-acyltransferase (acylacylation)	acACP + h + matACP => ACP + acACP	fadH or fadF1 or PA3174	0.75	0.44
Glutamine transaminase	glu-L + pyridox => akg + pyridox	glaA1 or glaA2	0.22	0.18
Alanine transaminase	ala-L + pyridox => pyridox + pyr	glaA1 or glaA2 or glaA3	0.37	0.29
3-keto-D-manno-octulosonic acid transferase	PA3 lipdA + cldo => PA3_XDolipdA + cmp + h	waaA	1.13	0.23
Phosphate transport via ABC system	atp + h2o + pte[] => atp + h + 2 pi	pstABCS	0.24	0.27
L-serine deaminase	ser-L <=> rml + pyr	sdhA3	0.45	0.26
O-succinylhomoserine lyase (HIS)	h2o + succoa => h2p-L + succ	rmlC	0.58	0.44
Up-regulated				
Pst synthesis ^c	3 gtpman + udg + dtdpman => pte[] + 3 gtp + udg + dtdp	pstACDEFHJLKL	0.88	2.87
Anthranilate 1,2-dioxygenase	anrh + nadph + 2 h + o2 => catechol + co2 + nadp + h2o	antA	5.64	2.48
3-oxoadipyl-CoA thioesterase	coa + oxaadpcoo => accoa + succoa	pcaF	1.93	2.06
Catechol 1,2-dioxygenase	catechol + o2 => rmlc	catA	4.30	2.48
3-oxoadipate endolactonase	3oxadpa + h2o => 3oxadp + h	pcaD	3.16	2.06
3-oxoadipate CoA-transferase	3oxadp + succoa <=> oxaadpcoo + succ	dhaA9	0.92	2.06
NAD(P) transhydrogenase	2 h[] + nadh + nadp <=> 2 h + nad	pntA4 and pntB	1.12	3.51
Isochorismate synthase	chor => khor	pchA	6.24	3.91
Isochorismate-pyruvate lyase	ichor => sal + pyr	pchB	7.86	3.91
Pyochelin synthase pchE	cys-L + atp => cysamp + ppi	pchE	6.97	3.91
Pyochelin synthase pchD	sal + atp + h => salamp + ppi	pchD	3.30	3.91
Pyochelin synthase pchOG	salamp + cysamp => hphthiazoline + 2 amp + h2o + h	pchOG	2.73	3.91
Pyochelin synthase pchEF	hphthiazoline + cysamp => hphthiazoline + 2 amp + h2o + h	pchEF	3.86	3.91
Pyochelin synthase pchGF	hphthiazoline + nadph + h => dmpyochein + nadp	pchGF	1.94	3.91
Pyochelin synthase pchF	dmpyochein + met + h2o => pyochelin + ahpco + 3 h	pchF	1.66	3.91

^a GE ratio, gene expression ratio between biofilm and stationary planktonic conditions.^b The median, minimum (Min.) and maximum (Max.) values of the flux ratio of each reaction in the set of simulations carried out using each member of the ensemble of flux distributions.^c Biofilm-related reaction with considerable flux change but no significant gene expression changes.

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Fig 2.Expression of *pqs*, *pst*, and *pel* operons as a function of biofilm age.

(A) Correlation coefficient of the expression intensity of the genes in the *pqs*, *pst*, and *pel* operons and biofilm age (h). (B) Expression of one gene from each operon as a function of biofilm age. Gene expressions are shown in log₂ scale. Each dot corresponds to one condition in the dataset of gene expression for *P. aeruginosa* PAO1 biofilms. The circles correspond to the data obtained by Costaglioli et al. [11]. AU, arbitrary units; h, hours.

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