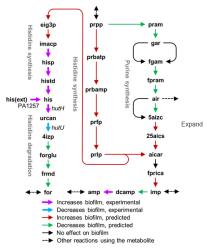
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## Fig 1.

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.

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### Table 1.

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

Reaction name	Reaction	Genes	Identification method <sup>a</sup>				
Reduced antimicrobial tolerance							
N-acetyl-g-glutarnyl-phosphate reductase	acg5sa + nadp + pi < = > acg5p + h + nadph	argC	Р				
Formimidoylglutamase	forglu + h2o = > frmd + glu-L	hutG or PA3175	P				
	Attenuated virulence						
1,2-diacyl-sn-glycerol 3-phosphate synthesis	1.02 2tocdACP + glyc3p + 0.26 hdeACP + 0.06 ocdACP + 0.66 palmACP = > 12dag3p_PA + 2 ACP	(plsY or plsX or plsB) and ([ptA or olsA)	Е				
Isochorismate Synthase	chor = > ichor	pchA	E				
Orotidine-5-phosphate decarboxytase	h + orot5p = > co2 + ump	pyrF	Е				
Protoporphyrinogen oxidase	1.5 o2 + pppg9 = > 3 h2o + ppp9	hemY or hemK	E	Expa			
Arginine N-succinyltransferase	arg-L + succoa = > sucarg + coa + h	aruF and aruG	E				
1-hydroxyphenazine synthase	h + nadh + o2 + pca = > 1hphe + co2 + h2o + nad	phzS	P				
Phenazine-1-carboxylic acid synthesis, step 1	chor + gln-L = > a4dic + glu-L	phzE1 or phzE2	Р				
Phenazine-1-carboxylic acid synthesis, step 2	a4dic + h2o = > dhha + h + pyr	phzD1 or phzD2	Р				
Rhamnosyltransferase chain A	3hdeACP + coa = > 3hdccoa + ACP	rh(A	P				
Isochorismate-pyruvate Iyase	ichor = > sal + pyr	pchB	P				
Pyochelin synthesis pchDG	salamp + cysamp = > hpthiazoline + 2 amp + h2o + h	pchG and pchD	P				

# Table 2.

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

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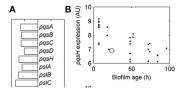
Reaction name	Reaction	Genes	GE ratio*	Flux ratio <sup>b</sup>			
				Median	Min.	Max.	
	Down-regulated						
HHQ synthesis <sup>4</sup>	3oxdeACP + anth + h = > ACP + co2 + h2o + hhq	pqsABCD	0.60	0.47	0.33	0.79	
Probable FAD-dependent monooxygenase [PQS synthesis] <sup>2</sup>	fadh2 + hhq + o2 = > fad + h2o + pqs	pqsH	0.99	0.47	0.33	0.79	
Acyl-ACP:malonyl-ACP C-acyltransferase (decarboxylating)	acACP + h + malACP = > ACP + actACP + co2	fabB or fabF1 or PA5174	0.75	0.44	0.25	0.77	
Glutamine transaminase	glu-L + pydx5p = > akg + pyam5p	glyA1 or glyA2	0.22	0.18	0.15	0.34	
Alanine transaminase	ala-L + pydx5p = > pyam5p + pyr	glyA1 or glyA2 or glyA3	0.37	0.29	0.24	0.57	
3-deoxy-D-manno-octulosonic acid ransferase	PA_lipidA + ckdo = > PA_KDOlipidA + cmp + h	wasA	1.13	0.23	0.08	0.74	
Phosphate transport via ABC system	atp + h2o + pi[e] = > adp + h + 2 pi	pstABCS	0.24	0.27	0.25	0.34	
-serine deaminase	ser-L <= > nh4 + pyr	sdsAB	0.45	0.28	0.09	0.43	
O-succiry/homoserine lyase (H2S)	h2s + suchms = > hoys-L + succ	metZ	0.58	0.44	0.35	0.57	
	Up-regulated						
PsI synthesis <sup>c</sup>	3 gdpman + udpg + dtdp6dm = > psl(e) + 3 gdp + udp + dtdp	psIACDEFGHIJKL	0.88	2.87	1.22	6.86	
Anthranilate 1,2-dioxygenase	anth + nadph + 2 h + o2 = > catechol + co2 + nadp + nh3	antA	5.64	2.48	1.90	6.01	
3-oxoadipyl-CoA thiolase	coa + oxadpcoa = > accoa + succoa	pcaF	1.93	2.06	1.32	3.24	Expar
Catechol 1,2-dioxygenase	catechol + o2 = > muc	cetA	4.30	2.48	1.90	6.01	
3-oxoadipate enol-lactonase	5odhf2a + h2o < = > 3oxadp + h	pcaD	3.16	2.06	1.32	3.24	
3-oxoadipate CoA-transferase	3oxadp + succoa < = > oxadpcoa + succ	dhcAB	0.92	2.06	1.32	3.24	
NAD(P) transhydrogenase	2 h(e) + nadh + nadp < = > 2 h + nad + nadph	pntAA and pntB	1.12	3.51	1.99	4.88	
sochorismate synthase	chor = > ichor	pchA	6.24	3.91	3.46	4.22	
Isochorismate-pyruvate Iyase	ichor = > sal + pyr	pchB	7.86	3.91	3.46	4.22	
Pyochelin synthesis pchE	cys-L + atp = > cysamp + ppi	pchE	8.97	3.91	3.46	4.22	
Pyochelin synthesis pchD	sal + atp + h = > salamp + ppi	pchD	3.30	3.91	3.46	4.22	
Pyochelin synthesis pchDG	salamp + cysamp = > hpthiazoline + 2 amp + h2o + h	pchDG	2.73	3.91	3.46	4.22	
Pyochelin synthesis pchEF	hpthiazoline + cysamp = > hpbthiazoline + amp + h2o + h	pchEF	3.86	3.91	3.46	4.22	
Pyochelin synthesis pchGF	hpbthiazoline + nadph + h = > dmpyochelin + nadp	pchGF	1.94	3.91	3.46	4.22	
Pyochelin synthesis pchF	dmpyochelin + amet + h2o = > pyochelin + ahcvs + 3 h	pchF	1.66	3.91	3.46	4.22	

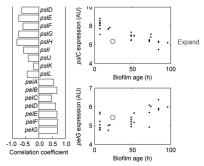
# Fig 2.

Expression of pqs, psl, and pel operons as a function of biofilm age.

(A) Correlation coefficient of the expression intensity of the genes in the pqs, psl, 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 log, 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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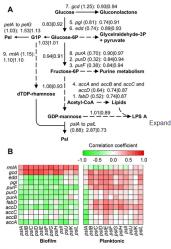


### Fig 3.

Coordinated regulation of Psl synthesis.

(A) Sketch of the metabolic pathways involved in the increase of PsI and Pel production rates in our simulations. The figure shows the genes associated with the nine reactions that had the highest effect on Pel production. The number to the left of each gene name denotes the rank of the corresponding reaction. The number in parentheses denotes the vertal gene expression ratio between the biofilm and the stationary cultures. The numbers to the left and right of the vertical bar denote the median flux ratios of the reactions associated with the genes in simulation with or without the gene expression ratios of the genes accABCD, tabD, purADF, pol, edd, god, and rMA. Only psl, pel, and those genes whose regulation contributes to increasing PsI and Pel production are shown. (B) Correlation between the expression of the genes that contribute to increasing PsI production and the psI operon genes for biofilm and stationary cultures. Solid and dashed arrows indicate single and multiple reaction steps in the model, respectively.

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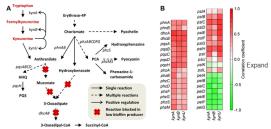


# Fig 4.

Dysregulation of secondary metabolites related to biofilm formation by inhibition of anthranilate degradation.

(A) Sketch of the metabolic pathways involved in anthranilate and chorismate metabolism. Metabolite names written in red were predicted to increase when the reactions marked with a red x, which correspond to the low biofilim producers identified by Costaglioli et al. [11], were inhibited. (B) Correlation of the gene expression intensity of genes associated with anthranilate- and chorismate-derived secondary metabolites, ps/ and pel genes, with the genes of the bourseins positive.

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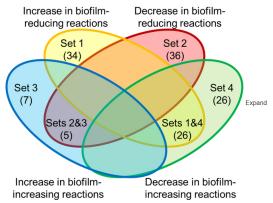


# Fig 5.

Definition of metabolite sets whose concentration changes were specific to either biofilm-reducing or biofilm-increasing reactions

The defined sets are as follows: set 1, metabolites that specifically increased when inhibiting biofilm-reducing reactions; set 2, metabolites that specifically decreased when inhibiting biofilm-increasing reactions; set 3, metabolites that specifically increased when inhibiting biofilm-increasing reactions; and set 4, metabolites that decreased when inhibiting biofilm-increasing reactions. Note that each metabolite set includes metabolites from two subsets of the Ven diagram. The number in parentheses indicates the number of metabolites in each subset.

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