# Exploring gene expression in *Yersinia pestis*

In 541-542, a plague swept in and killed 40% of the population in Europe. Almost 100 years later, a similar plague, infamously referred to as "The Black Death"



resulted in the deaths of an estimated 75 to 200 million people, or 30% of the European population, with the epidemic peaking in Europe in the years 1346–53[1]. In 1894, Alexandre Yersin, a Swiss/French physician and bacteriologist from the Pasteur Institute, discovered the bacterium that caused plague, and the organism was named *Yersinia pestis* in his honor in 1967[2]. This bacterium is small, rod-shaped, and is able to infect both fleas and mammals. The bacterium must survive in both hosts to infect humans, as in most cases it is transmitted by the bite of an infected flea.

Fleas have a body temperature of 26°C, while the human body temperature is 37°C. Scientists wanted to explore what genes *Y. pestis* turned on (called up-regulated) and turned off (called down-regulated) at these two temperatures. They looked specifically at a strain of *Y. pestis* that they had made mutant at one critical gene, called Lpp, which was essential for survival in the mammal host[3].

We will examine this experiment and, using PATRIC tools, we will explore the upand down-regulation of genes at the two different temperatures.

### I. Exploring an experiment

1. Login to the PATRIC website so that you can use your workspace in the downstream analysis.



2. On the PATRIC homepage (patricbrc.org), open the Organisms tab at the top of the page.



3. When the tab opens to reveal the box listing the names of pathogens, click on Yersinia.

ORGANISMS	DATA	SERVICES	TOOLS								
Genera Containing NIAID Category A-C / Emerging / Re-emerging Bacteria Pathogens											
Bacillus		Francisella									
Bartonella		+ Helicobacte	er								
Borrelia		• Listeria									
Brucella		Mycobacter	rium								
• Burkholderia		Rickettsia									
Campylobact	ter	Salmonella									
Chlamydoph	ila	• Shigella									
Clostridium		Staphylococcus									
Coxiella		• Streptococi	cus								
Ehrlichia		Vibrio									
• Escherichia		Yersinia									
Complete Lists of Bacteria:											
All Bacteria											
All Archaea											

4. This will take you to the landing page for *Yersinia*, which summarizes all the information that PATRIC has about the genus, including the number of genomes, experiments associated with it, publications on it, and tools that can analyze the available data sorted at that taxonomic level.

Bacteria * Proteobacteria * Garr	nmaproteo	bacteria • En	terobacterial	es • Enterot	acteriaceae • 1	rersinia ⊞				Dat	a Overview Tutorial » vnload genome data
Overview Taxonomy Ph	iylogeny	Genome List	Feature Table	Specialty Genes	Protein Families	Pathways	Transcriptomics	Interactions	Diseases	Literature	
Search Tools		Тахо	nomy Sum	mary							
GE Genome Finder		Taxon	omy ID	62	2						
Feature Finder	bol	Linea	je -	<u>ce</u>	lular organisms Yersinia	> <u>Bacteria</u> > P	roteobacteria > G	ammaproteobad	teria > Enter	obacteriales > I	Enterobacteriaceae
Distance Fundance - Contract		Extern	nal Links	Im	mune Epitope C	atabase and A	nalysis Resource				
Protein ranny Sorter		Summ	nary Terms - C	lick on numb	er to view geno	mes associated	with term (see P)	TRIC FAQs)			
Experiment Summary		Genor	me Status	W	GS ( <u>130</u> ), Com	plete ( <u>44</u> )					
Transcriptomics from GEO	81	Refere	ence Genome	R	epresentative (1	2), Reference	(2)				
Transcriptomics from	57	Antim	icrobial Resist	ance							
ArrayExpress	20	Antim	icrobial Resist	ance							
Proteomics from PRIDE	(	) Evider	nce								
Structure from NCBI	290	Isolat	ion Country	Pr	ru ( <u>60</u> ), USA (	19), show all 1	28 genomes				
Protein Protein Interaction from	4060	Host I	Name	н	uman, Homo sa	piens (38), Bla	ck rat, Rattus ratti	is (16), show a	all 110 genom	es	
IntAct	-1005	Disea	se	В	ubonic plague (§	33), Pneumoni	c plague ( <u>60</u> ), sho	w all 217 geno	mes		
more >		Collec	tion Date	20	10 (45), 2009	(13), show all	100 genomes				
Recent PubMed Articles		Comp	letion Date	20	012 (73), 2013	(24), show all	174 genomes				

5. Find the tab across the top that is labeled "Transcriptomics" and click on it.

Bacteria • Pro	teobacteria •	Gammaprotec	bacteria • En	terobacterial	es ⊦ Enterobac	teriaceae + Yo	ersinia 🗄	
Overview	Taxonomy	Phylogeny	Genome List	Feature Table	Specialty Genes	Protein Families	Pathways	Transcriptomics

6. This will take you to the landing page for the transcriptomics experiments that are available through the PATRIC resource. The left side has a filter to help people find specific experiments, and on the right is a table that summarizes the experiments available.

		Overview	Taxonomy	Phylogeny	Genome List	Feature Table	Specialty Genes	Protein Families	athways	Transcriptomic	Interactions	Diseases Literature		
The list below provides all of the available ransciptomics data and associated metac	e transc lata, se	riptomics ex e <u>Transcript</u>	periments omics FAQ	and associate	ed metadat	a at this taxe	onomic level. 1	'he list of expe	riments o	an be filtered b	y metadata c	or keyword. To learn mon	e about PATH	uc's
Filter By 🤃	Expe	riments (	comparison	5										
keyword Clear All	6 exp	periments	found											
Organism (7)		Workspace		View	D	boolnwo	0	olumns						
Yersinia pestis (6)	Ad	id Experimenti	s) 🔳	Gene List		Table -	o Show/	lide - Defa	it					
Yersinia pseudotuberculosis (1) Strain (8)		Title +						Comparisons	Genes	PubMed	Link Out	Organism	Strain	Gene Modifi
201 (3)	0	Comparative tr	anscriptomic	s in Yersinia pes	tis: a global	view of environ	nmental modula.	24	3655	17963531	GSE9279	Yersinia pestis	201	fur,ompR,
C092 (2)	0	Gene expressio	in analysis of	Yersinia Pestis	temperature	shift.		12	28357	22479471	GSE30634	Yersinia pestis, Yersinia ps	CO92,PB1	
PB1/+ (1)	0	Gene expressio	n profiles of	wild-type Yersin	nia pestis COS	2 and its Brau	n lipoprotein m	2	7655	20508723	GSE19840	Yersinia pestis	C092	LPP
more	E 1	Involvement of	the post-tra	nscriptional reg	ulator Hfg in	Yersinia pestis	virulence	1	3655	2704395	GSE15579	Yersinia pestis	201	hfq
Gene Modification (7)	E 1	CIM5 intracelly	lar expressio	n profiling				6	7834	20565693	GSE22168	Yersinia pestis	KIM5	
CompR (2)	E 1	Phenotypic and	transcriptio	nal analysis of t	he osmotic re	quiator OmpR	in Yersinia pesti	1	3704	21345178	GSE26601	Yersinia pestis	201	ompR

7. Find the experiment with the title "Gene expression profiles of wild-type Yersinia pestis CO92 and its Braun lipoprotein mutant at flea and human temp" and click the check box in front of it.

	Title 🛎
	Comparative transcriptomics in Yersinia pestis: a global view of environmental modula
	Gene expression analysis of Yersinia Pestis temperature shift.
	Gene expression profiles of wild-type Yersinia pestis CO92 and its Braun lipoprotein m
	Involvement of the post-transcriptional regulator Hfq in Yersinia pestis virulence
	KIM5 intracellular expression profiling
	Phenotypic and transcriptional analysis of the osmotic regulator OmpR in Yersinia pestis
1	

8. Next, in the header across the top of the table in the category called "View" click on the "Gene List" tool.



9. This will take you to the Transcriptomics Gene list for the experiment that you chose. There is a filter on the right side, and a table that will show the results of the filter on the left. When the page opens up and before any actions are taken, all genes available in the experiment are listed in the table.

Filter By			~	Table	e Heatmap								
comparison(s)	in 1 exp	eriment(s)		7655	genes found								
1 ↓ 1↓	Source	Title	Strain		Workspace	View	Download		Toc	ols	Columns		Help
000	PATRIC PATRIC	Yersinia pestis C Yersinia pestis C	CO92 CO92	22	Add Feature(s)	FASTA DNA	Table FASTA	<ul> <li>Pathy</li> <li>MAJ</li> </ul>	vay Summary 🔡 P IDs to 👻	Multiple Seq Alignment	Show/Hide	<ul> <li>Default</li> </ul>	
					Genome Name 🐣	PATRIC ID	RefSeq Locus T	Alt Locus Tag	Gene Symbol	Product Description	Comparisons	Up	Down
					Yersinia pestis CO92	fig 214092	YPO0001	VBIYerPes7		Flavoprotein MioC	2	0	2
					Yersinia pestis CO92	fig]214092	YPO0002	VBIYerPes7	asnC	Regulatory protein AsnC	2	1	1
				0	Yersinia pestis CO92	fig 214092	YPO0003	VBIYerPes7	asnA	Aspartateammonia ligase	: ( 2	1	0
Filter by					Yersinia pestis CO92	fig 214092	YP00004	VBIYerPes7	yieM	FIG01221722: hypothetica	l p 2	1	1
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Filter by one or i	more kevy	ords or locus taos		17	Yersinia pestis CO92	fig]214092	YPO0006	VBIYerPes7	trkD	Kup system potassium upt	ak 2	2	0
					Yersinia pestis CO92	fig 214092	YPO0007	VBIYerPes7		Ribose ABC transport syste	em 2	0	2
				1	Yersinia pestis CO92	fig 214092	YPO0008	VBIYerPes7	rbsK	Ribokinase (EC 2.7.1.15)	2	0	2
				<b>F</b> . •	Yersinia pestis CO92	fig]214092	YPO0009	VBIYerPes7		Permeases of the major fa	cili 2	1	1
				10	Yersinia pestis CO92	fig 214092	YPO0010	VBIYerPes7		Transcriptional regulator, O	int 2	2	0
e.g. VBIEscCol1	9921_000	1, Transcription fa	actor		Yersinia pestis CO92	fig 214092	YPO0011	VBIYerPes7		Mobile element protein	2	2	0
				10	Yersinia pestis CO92	fig 214092	YPO0012	VBIYerPes7	mobB	Molybdopterin-guanine dir	uc 2	1	1
Filter by  Log Ra	tio]:	*		E .	Yersinia pestis CO92	fig 214092	YPO0013	VBIYerPes7	mobA	Molybdopterin-guanine dir	uc 2	1	1
Filter by Z-score	:	*			Yersinia pestis CO92	fig 214092	YPO0013a	VBIYerPes7		Protein yihD	2	1	1
100 No.	6 ( ) ( ) ( )		-	1	Yersinia pestis CO92	fig 214092	YPO0014	VBIYerPes7		YihE protein, a ser/thr kina	ise 2	2	0
			Filter	1	Yersinia pestis CO92	fig 214092	YPO0015	VBIYerPes7	dsbA	Periplasmic thiol:disulfide i	nt 2	2	0
				100	Yersinia pestis CO92	fig1214092	YPO0017	VBIYerPes7	Alog	DNA polymerase I (EC 2.7	77) 2	2	0

10. To find the experimental conditions and see the two different temperatures, you will first need to expand the filter box by grabbing the right edge with your cursor and then increasing the width of the box.

Filte	er By							«	Tab
! cor	nparis	on(s)	in 1 exp	eriment(s)					765
1	Ļ	ţţ	Source	Title	Strain	Modification	Condition	Time Point	
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0	$\bigcirc$	0	PATRIC	Yersinia pestis C	CO92	LPP	mutant vs wild t		
Filte	er bv								
Ger	nome :				•				

11. Then you will have to grab the right edge of the column header called "Title" and use your cursor to increase the width of that box. Then you will be able to see which experimental condition was done at  $26^{\circ}$ C, and which at  $37^{\circ}$ C.

	Filte	r By				«
2	con	nparis	on(s)	in 1 exp	eriment(s)	
	1	ţ	1↓	Source	Title	Strain
	0	$\bigcirc$	0	PATRIC	Yersinia pestis CO92 LPP mutant cultured at 26C / Yersinia pestis CO92 wild-type $\ldots$	CO92
	0	$\bigcirc$	0	PATRIC	Yersinia pestis CO92 LPP mutant cultured at 37C / Yersinia pestis CO92 wild-type $\ldots$	CO92

12. To see which genes are up-regulated at 26°C and down-regulated at 37°C, click the up arrow on the 26C row, and the down arrow on the row for 37C.

Filter	ву			(*)
2 com	parise	on(s)	in 1 exp	eriment(s)
1	Ļ	ţ↑	Source	Title
0	$\bigcirc$	$\bigcirc$	PATRIC	Yersinia pestis CO92 LPP mutant cultured at 26C / Yersinia pes
0	0	$\bigcirc$	PATRIC	Yersinia pestis CO92 LPP mutant cultured at 37C / Yersinia pes

13. You will want to see which genes are significantly expressed. To do this, look at the bottom of the filter, and where is says "Filter by |Log Ratio|:" there is an arrow. Click the arrow and you will see a box with numbers in it. Choose 1, and this will give you a fold-change of two (log2). Then click "Filter".



14. This will filter the table to show that there are 38 genes that meet those criteria. These genes are up-regulated at 26C (the temperature of the flea host) and down regulated at 37C (the temperature of the human host).

	,				•				,	
Tab	le Heatmap									
38 9	genes found									
	Workspace	View		Do	wnload			Tools		Columns
Ŕ	Add Feature(s)	₿ FASTA DN S FASTA Pro	A tein		Table - FASTA -	t X	Pathway Summar MAP IDs to	y Eth Multiple Sec	Alignment	Show/Hide
	Genome Name 🔺		PATRIC	ID	RefSeq Loc	us Tag	Alt Locus Tag	Gene Symbol	Product Des	cription
	Yersinia pestis CO92		fig 2140	92.21	YPO0163		VBIYerPes784		TsgA proteir	1 homolog
	Yersinia pestis CO92		fig 2140	92.21	YPO0222		VBIYerPes784	rpIE	LSU ribosom	nal protein L5p (L11e)
	Yersinia pestis CO92		fig 2140	92.21	YPO0224		VBIYerPes784	rplF	LSU ribosom	nal protein L6p (L9e)
	Yersinia pestis CO92		fig 2140	92.21	YPO0444		VBIYerPes784	nadR	NadR transc	criptional regulator /
	Yersinia pestis CO92		fig 2140	92.21	YPO1142		VBIYerPes784	modF	Putative mo	lybdenum transport A
	Yersinia pestis CO92		fig 2140	92.21	YPO1168		VBIYerPes784	betT	High-affinity	choline uptake prote
	Yersinia nestis CO92		figl2140	92.21.	YPO1326		VBIYerPes784		TrkA. Potass	sium channel-family n

15. To see all the genes, you will need to scroll down to the bottom of the table and resize it to 38 and hit return.

A Page 1 of 2 Page Show 38 per page	II of 2 ► ►	Show 38	per page
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16. To visualize these genes, PATRIC provides a heatmap view. To see the genes, click on the "Heatmap" tab.



17. You will notice that there are two columns. One is varying degrees of red, and the other is varying degrees of green. The red color signifies up-regulation, so this is the 26C column. Green is down-regulation (37C).



18. To get more details on specific genes, you can mouse a single cell of interest. I moused over a light green box in the 37C. When you do that, you can see details on that gene in the blue band at the top of the heatmap. In this example, that gene is the "Outer membrane protein C precursor" that is strongly down-regulated with a log ratio of -4.228.



### II. Discovering if genes of interest have any functional significance.

1. From the previous example, return to the table by clicking on the Table tab.



2. In the column titled "Genome Name", click on the box to the left of it select all the genes

Tat	e Heatmap										
38 genes found											
	Workspace	V	iew								
<b>**</b>		🍃 FASTA	DNA								
		🔊 Fasta	Protein	8							
1	Genome Name 📥		PATRIC ID								
<b>V</b>	Yersinia pestis CO92		fig 214092.								
<b>V</b>	Yersinia pestis CO92		fig 214092.								
<b>V</b>	Yersinia pestis CO92		fig 214092.								

3. We need to save these features to a workspace. Click on the "Add Feature" and folder.



4. This will open up a pop-up window that allows you to save the group.



5. Select the "Create New Group" option.

Add Selected Feature(s) to Workspace									
Save as Feature Group     Save as Genome Group									
Add to group: None									
New group nam None									
	Create New Group								
	TBDream genes								
	EmbB_1070								
EmbB_1094									
fig 2140	India-tuberculosis-FIG01954080-1095								

6. Name the group and click "Save to Workspace". Now that data is saved and you can use a number of tools to explore it.



7. This data is now safely in the Workspace, but we can also examine it here from this table. To look at the data with the Pathway tool, you first need to select all the features in this table again.



8. Once the genes are selected, you can use the Pathway Summary tool that you can see at the top of the table under the Tools heading. Click on that.



9. This will return a table that shows you the list of pathways that the genes you selected are involved in.

athwo	ay Summary									
out of :	38 genes sele	cted, 5 genes four	nd in 5 pathway	s						
١	Norkspace	View	Download			Toois	Columns			
	Add Feature(s)	FASTA DNA	Table FASTA	:	MAP IDs to	y III Multiple Seq Alignment	Show/Hide - Default			
Pathway Name						# of Genes Selected		# of Genes Annotated		
E n	niamine metabolis	n				1	20			
	idative phosphory	lation				2	58			
G	vcerolipid metabol	lism				1	36			
	Nitrogen metabolism					2	75			
E No	Nicotinate and nicotinamide metabolism					1	41			

10. Clicking on any of the pathway names in the table will take you to a KEGG map that shows how many the genes you selected acted as enzymes are involved in that pathway.



## III. Exploring specific genes that are significantly expressed in an experiment

1. In the heatmap view above we saw that a gene called "Outer membrane protein C precursor" was strongly down-regulated at 37°C. Return to the workspace by clicking on Workspace at the top of the page.



2. We're going to return to the group created earlier, so double-click on the name Feature Groups as you did before.



3. Once again, double-click on the name you selected for your group. I called mine "Yersinia pestis up-regulated at 26C".

Wo	kshop / home / Feature Groups			1 D	0	Yersinia pestis
	Name	Size	Owner	Created	*	up-regulated at 26C
t	Parent Folder				m	Type: feature_group
	EmbB_1070	160 features	Workshop	4/14/15, 3:56 PM		Owner: Workshop@patricbrc.org
	EmbB_1094	90 features	Workshop	4/14/15, 3:57 PM		Path:
	India-tuberculosis-FIG01954080-1095	125 features	Workshop	4/14/15, 7:33 PM		/Workshop@patricbrc.org/home/Feature
-	TBDream genes	1348 features	Workshop	4/14/15, 3:08 PM		Groups rersina pesiis upreguated at 200
	Yersinia pestis genes up-regulated at 37C	43 features	Workshop	4/17/15, 6:22 PM		
	Yersinia pestis up-regulated at 26C	58 features	Workshop	4/17/15, 3:49 PM		
	Yersinia pestis up-regulated at 26C Arlington	38 features	Workshop	5/2/15, 6:46 PM		

4. Scroll down until you see the gene called "Outer membrane protein C precursor" and click on it once to select it.

Genome Name	PATRIC ID	RefSeq Locus Tag	Alt Locus Tag	Gene Symbol	Product C
Yersinia pestis CO92	fig 214092.21.peg.688	YP00444	VBIYerPes7843_0688	nadR	NadR transcriptional regulator / Nicotinamide- nucleotide adenylyltransferase, NadR family (EC 2.7.7.1) / Ribosylnicotinamide kinase (EC 2.7.1.22)
Yersinia pestis CO92	fig 214092.21.peg.1437	YPO1142	VBIYerPes7843_1437	modF	Putative molybdenum transport ATP-binding protein modF
Yersinia pestis CO92	fig 214092.21.peg.1465	YPO1168	VBIYerPes7843_1465	betT	High-affinity choline uptake protein BetT
Yersinia pestis CO92	fig 214092.21.peg.1641	YPO1326	VBIYerPes7843_1641		TrkA, Potassium channel-family protein
Yersinia pestis CO92	fig 214092.21.peg.1738	YPO1411	VBIYerPes7843_1738	ompF	Outer membrane protein C precursor

5. When you click on it, the description panel to the right shows information related to the gene. The informative band that separates the table from the description panel also shows tools that you can use with your selection.

Image: Section of the section of th		_		
ProductAccessionNC_003143L6p (L9e)start1599145NadR transcriptional regulator / Nicotinamide- nucleotide adenylyltransferase, NadR family (EC 2.7.7.1) / Ribosylnicotinamide kinase (EC 2.7.1.22)productOuter membrane protein C precursor genome_id218928559 gene gene ompF218928559 gene ompF218928559 gene ompF2.7.7.1) / Ribosylnicotinamide kinase (EC 2.7.1.22)Putative molybdenum transport ATP-binding protein modF1083 strand - refseq_locus_tagVBIYerPes7843_1738 tagents tagents tagents tagents tagentsHigh-affinity choline uptake protein BetTFig02 taxon_id talength214092 taxon_id talength tagents tagentsOuter membrane protein C precursorgenome_name tagents tagentsYP-002346434.1 tag_le1092.21.peg.1738 tagents tagentsOuter membrane protein C precursorgenome_name tagentsYP-002346434.1 tag_le1092.21.peg.1738 tagentsOuter membrane protein C precursorgenome_name tagentsYP-002346434.1 tag_lengthOuter membrane protein C precursorgenome_name tagentsYersinia pestis CO92 publicOuter membrane protein C precursorgenome_name tagentsYersinia pestis CO92 public	<b>.</b>	0	location gene_id	complement(15991451600227) 1174252
Productstart1599145L6p (L9e)start1599145NadR transcriptional regulator / Nicotinamide- nucleotide adenylyltransferase, NadR family (EC 2.7.7.1) / 	-		accession	NC_003143
L6p (L9e)feature_idPATRIC.214092.21.NC_003143.CDS.159NadR transcriptional regulator / Nicotinamide- nucleotide adenylyltransferase, NadR family (EC 2.7.7.1) / Ribosylnicotinamide transport ATP-binding protein modFproductOuter membrane protein C precursor genome_id2100 2110 2110 2110 2110 2110 2110 2110 2110 2110 2110 2110productOuter membrane protein C precursor2110 2110 2110 2110 2110 2110 2110productOuter membrane protein genome_id214092.21 214092.21 product2111 2110 2110 2110 2110 2110 2110 2110 2110productOuter membrane protein pos_groupproduct2110 2110 2110 2110 2110productPatric.214092.21 214092.21 214092 2110 214092 2110product2110 2110 2110 2110 2110productproductproduct2110 2110 2110productproductproduct2110 2110 2110productproductproduct2110 2110 2110productproductproduct2110 2110 2110productproductproduct2110 2110productproductproduct2110 2110productproductproduct2110 2110productproductproduct2110 2110productproductproduct2110 2110productproductproduct2110 2110productproductproduct2110 	Product 0	$\odot$	start	1599145
NadR transcriptional regulator / Nicotinamide- nucleotide adenylyltransferase, NadR family (EC 2.7.7.1) / Ribosylnicotinamide kinase (EC 2.7.1.22)sequence_id product (imported to the sequence) outport of the sequence	L6p (L9e)	-	feature_id	PATRIC.214092.21.NC_003143.CDS.159
Nadok transcriptional regulator / Nicotinamide- nucleotide adenylyltransferase, NadR family (EC 2.7.7.1) / Ribosylnicotinamide kinase (EC 2.7.1.22)annotation productPATRIC Outer membrane protein C precursor genome_idPutative molybdenum transport ATP-binding protein modFImage: Complexity of the section of the sec	NedD transmistional	6	sequence_id	NC_003143
regulator /Nicotinamide- nucleotideproductOuter membrane protein C precursoradenylyltransferase, adenylyltransferase, NadR family (EC 2.7.7.1) /uniprotkb_accessionQ0WH04 gi218928559 gene2.7.7.1) / Ribosylnicotinamide kinase (EC 2.7.1.22)p2_feature_id108115791 pos_groupPutative molybdenum transport ATP-binding protein modF-High-affinity choline uptake protein BetT-TrrkA, Potassium channel-family protein-Outer membrane protein C precursor-Outer membrane protein C precursor-Putative molybdenum transport ATP-binding protein modF-Figh-affinity choline uptake protein BetT-TrrkA, Potassium channel-family protein-Outer membrane protein C precursor-Public ctrue owmerPutative molybdenum transport ATP-binding protein modFHigh-affinity choline uptake protein BetT-TrrkA, Potassium channel-family protein-Outer membrane protein C precursor-Outer membrane protein C precursor- </td <td>NadR transcriptional</td> <td>Sector</td> <td>annotation</td> <td>PATRIC</td>	NadR transcriptional	Sector	annotation	PATRIC
Nicotinamide- nucleotide adenylyltransferase, NadR family (EC 2.7.7.1) / Ribosylnicotinamide kinase (EC 2.7.1.22)genome_id214092.21 figfam_idFIGO0633937 uniprotkb_accessionQ0WH04 gi218928559 gene ompFPutative molybdenum transport ATP-binding protein modFP2108115791 pos_groupNC_003143:1599145:- alt_locus_tag108115791 voll411High-affinity choline uptake protein BetTP2feature_type feature_typeCDS taxon_id214092 214092 voll411TrrkA, Potassium channel-family proteinOuter membrane protein C precursor9900227 feature_typeOuter membrane protein C precursor991080227 resinia pestis CO92 public1080227 feature_typeOuter membrane protein C precursor9991080227 feature_typeOuter membrane protein C precursor999Outer membrane protein C precursor <td>regulator /</td> <td>&gt;fasta</td> <td>product</td> <td>Outer membrane protein C precursor</td>	regulator /	>fasta	product	Outer membrane protein C precursor
nucleotidefigfam_idFIG00633937adenylyltransferase, NadR family (ECuniprotkb_accessionQ0WH042.7.7.1) / Ribosylnicotinamide kinase (EC 2.7.1.22)geneompFPutative molybdenum transport ATP-binding protein modFD2 feature_id108115791High-affinity choline uptake protein BetTrefseq_locus_tagYBIYerPes7843_1738 na_length1083 strandTrrkA, Potassium channel-family proteinOuter membrane protein C precursorYE full214092 postinia for the postinia postis CO92 publicOuter membrane protein C precursorVer PatricYenia postis CO92 public	Nicotinamide-	ATCGCGG CTAGGAT	genome_id	214092.21
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2.7.7.1) /       P2_feature_id       108115791         Ribosylnicotinamide       pos_group       NC_003143:1599145:-         kinase (EC 2.7.1.22)       alt_locus_tag       VBIYerPes7843_1738         Putative molybdenum       at_locus_tag       VBIYerPes7843_1738         transport ATP-binding       protein modF       1083         High-affinity choline       yptake protein BetT       15991451600227         TrrkA, Potassium       channel-family protein       214092         Outer membrane       ypotic       figl214092.21.peg.1738         protein C precursor       Yenome_name       Yersinia pestis CO92         public       true       owner       PATRIC	NadR family (EC	-	gene	ompF
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High-affinity choline       taxon_id       214092         uptake protein BetT       protein_id       YP_002346434.1         aa_length       360         channel-family protein       seed_id       figl214092.21.peg.1738         outer membrane       genome_name       Yersinia pestis CO92         public       true       owner       PATRIC	-		feature_type	CDS
uptake protein BetT     protein_id     YP_002346434.1       TrkA, Potassium     aa_length     360       channel-family protein     seed_id     fig]214092.21.peg.1738       Outer membrane     genome_name     Yersinia pestis CO92       public     true       owner     PATRIC	High-affinity choline		taxon_id	214092
TrkA, Potassium     aa_length     360       channel-family protein     seed_id     figl214092.21.peg.1738       outer membrane     genome_name     Yersinia pestis CO92       public     true       owner     PATRIC	uptake protein BetT	~	protein_id	YP_002346434.1
Intx, Polassium     seed_id     fig 214092.21.peg.1738       channel-family protein     end     1600227       Outer membrane     genome_name     Yersinia pestis CO92       protein C precursor     public     true       owner     PATRIC			aa_length	360
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protein C precursor public true owner PATRIC	Outer membrane		genome_name	Yersinia pestis CO92
owner PATRIC	protoin C procursor		public	true
	protein o precursor		owner	PATRIC

6. Mouse over the icons in the band until you see one that says "View Feature" (it's the eyeball). Click on that.



7. This will take you to the landing page for that gene where all the information available for it in PATRIC is summarized, including its different gene identifiers, tools and resources that can be used to examine this gene, and any publications that might have been written about it.

Bacteria + Brotenhacteria + Cammanrotenhact	eria t Enterobact	orialoc + Ente	erobacteriao	aaa + Vercini	a + Versinia ne	etic COQ2 +			
bacteria · Proteobacteria · Gammaproteobact	ena · Enterobact	endles - chu	erobacteriaci	ede • rersini	a · reisinia pe	sus CO92 -			
fig 214092.21.peg.1738 YPO1411 V	BIYerPes7843_	_1738   om	pF   Outer	membrane	protein C p	recursor ±			
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Add PATRIC Feature to Workspace Gene ID PATRIC ID: fig]214092.21,peg.1738 RefSeq; YP01411 Alt Locus Tag: VBIYerRes7843_1738									
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STITCH: Chemical-Protein Interactions	RefSeq	YPO1411		1599145	1600227	1083	360	Outer membrane po	orin protein F
	Eunctional P	roperties							
Recent PubMed Articles	runchonur	i oper nes							
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2013 Nov     Outer membrane proteins ail and	EC Assignment	s	-						
OmpF of Yersinia pestis are involved	Outer memorane proteins all and OmpF of Yersinia pestis are involved FIGfam Assignments FIG00633937								

8. Along the top panel, click on the tab called "Transcriptomics."



9. This takes you to all the experimental evidence for these gene that is available in the PATRIC website. The page is broken down to show the expression pattern for the gene across all the available experiments, a list of those experiments, and a circular diagram that can display different experimental conditions. Above the diagrams you will see some tools that allow you to filter the experiments.



10. As in the example above, we are going to filter the experiments displayed by the level of expression. Next to |Log Ratio|:" there is an arrow. Click the arrow and you will see a box with numbers in it. Choose 1, and this will give you a fold-change of two (log2).



11. This will set the log ratio to 1, but to see the results you have to click the "Filter" button



12. This will filter the table and the graphs to show those results. To see a visual representation of the experimental conditions where this gene had this fold-change, click on the "Experimental Condition" button above the bar graph.

Strain	Gene Modification	Experimental Condition
=		

13. This will show you that the majority of the experimental conditions where this gene was significantly up- or down-regulated dealt with temperature.



14. You can also see that in the table that has been filtered to match the log ratio selection. You can also see the log ratio values. Note that many of them are negative, as we saw in the initial experiment we were looking at.

I	Title	PubMed	Accession	Strain	Gene Modific	Experimental Condition	Time Point	Avg Intensity	Log Ratio	Z-score
I	Yersinia pestis, OmpR mutant (high osmolarity), 30	17963531	GSE9279		ompR	mutant vs wild type	30 mins	0	-4.037	-8.279
I	Yersinia pestis, Exponential growth phase, TMH / Ye	17963531	GSE9279			growth media		0	-1.979	-2.294
I	Yersinia pestis, grown at 37 C / Yersinia pestis	17963531	GSE9279			temperature	3 hrs	0	-2.619	-2.323
I	Yersinia pestis, ompR mutant, high salinity, 30 min /	17963531	GSE9279		ompR	mutant vs wild type	30 mins	0	-1.68	-3.659
I	ompR null mutant (ompR) / WT	21345178	GSE26601		ompR	mutant vs wild type		0	-4.533	-6.363
I	Yersinia pestis, 10 degree, 1 hr / Yersinia pestis, bef	17963531	GSE9279			temperature	1 hrs	0	1.573	1.398
I	Yersinia pestis CO92 LPP mutant cultured at 26C / Y	20508723	GSE19840		LPP	mutant vs wild type,te		0	1.006	1.106
I	Yersinia pestis, Exponential phase, TMH / Yersinia p	17963531	GSE9279			growth phase		0	-1.073	-2.105
I	Yersinia pestis, phoP mutant, 10 M Mg2 / Yersinia p	17963531	GSE9279		phoP	mutant vs wild type		0	-2.116	-1.8
I	Yersinia pestis, 45 degree,10min / Yersinia pestis, 37	17963531	GSE9279			temperature	10 mins	0	-1.575	-1.733
I	COW5 Total RNA extracted after 1 hour at 37 degre	22479471	GSE30634			temperature	1 hrs	0	-1.9	-2.138
I	PBIB15 Total RNA extracted after 1 hour at 37 degre	22479471	GSE30634			temperature	1 hrs	0	-1.639	-2.846
I	PBIB15 Total RNA extracted after 2 hours at 37 degr	22479471	GSE30634			temperature	2 hrs	0	-1.998	-2.33
I	PBIB15 Total RNA extracted after 4 hours at 37 degr	<u>22479471</u>	GSE30634			temperature	4 hrs	0	-1.698	-3.053
I	PBIB15 Total RNA extracted after 8 hours at 37 degr	22479471	GSE30634			temperature	8 hrs	0	-1.925	-3.807
I	PestF Total RNA extracted after 2 hours at 37 degre	22479471	GSE30634			temperature	2 hrs	0	-2.171	-4.669
L										

15. To see what other genes have a similar expression pattern, scroll to the top of the page and select the Correlated Genes tab.

Bacteria • Prot	acteria · Proteobacteria · Gammaproteobacteria · Enterobacteriales · Enterobacteriaceae · Yersinia · Yersinia pestis CO92 ·									
fig   214092.	ig   214092.21.peg.1738   YPO1411   VBIYerPes7843_1738   ompF   Outer membrane protein C precursor 🗈									
Overview	Genome Browser	Compare Region Viewer	Pathways	Transcriptomics	Interactions	Correlated Genes	Literature			

16. The page that returns will show you what genes have a similar expression pattern to the gene we chose, Outer membrane protein C precursor.

-			0									<b>A</b>	-		
		Bacteria • Pro fig   214092	teobacteria	<ul> <li>Gammaprote</li> <li>38   YP0141:</li> </ul>	obacteria • 8 1   VBIYer	Enterobacteriales • Pes7843_1738	Enterobacteri ompF   Out	iaceae • Yersinia • Ye er membrane pro	rsinia pes tein C pr	stis CO92 • recursor 街					
		Overview	Genome Browser	Compare Region Viewer	Pathways	Transcriptomics	Interactions	Correlated Genes	ature						
Correlation Cut	off: 0.4 Correl	ation: positive		Filter											
294 features for	ind														
Workspace	View	Downloa	d		Tools			Columns							Help
Add Feature	(s) FASTA DNA	Table	1	Pathway Summ MAP IDs to	nary 🔠 Mi	ultiple Seq Alignmen	6	Show/Hide - Defa	uit					2	PATRIC FAQs
	Genome Name			PATRIC ID		Alt Locus	Tag	RefSeq	Locus Tag		Gene Symbol	Product Description	Correlation	*	Comparisons
10	Yersinia pestis CO92		figi214	092.21.peg.173	8	VBIYerPes784	3 1738	YP	21411		ompF	Outer membrane protein C precursor	1.000		46
	Yersinia pestis CO92		figi214	092.21.peg.415	1	VBIYerPes784	3 4151	YP	23649			4-carboxymuconolactone decarboxylase (EC 4.1.)	1.44) 0.690		46
10	Yersinia pestis CO92		fig 214	092.21.peg.322	4	VBIYerPes784	3 3224	YP	12778			Cell division inhibitor Sir1223 (YfcH in EC), contai	ins epi 0.678		46
E3	Yersinia pestis CO92		fig1214	4092.21.peg.878	l i	VBIYerPes784	3 0878	YP	0623			Aspartate aminotransferase (EC 2.6.1.1)	0.655		46
	Yersinia pestis CO92		69/214	4092.21.peg.768	l .	VBIYerPes784	3 0768	YP	10516			FIG01220427: hypothetical protein	0.644		46
E3	Yersinia pestis CO92		fig1214	092.21.peg.105	2	V8IYerPes784	3 1062	YP	10800			Metallo-beta-lactamase superfamily protein PA00	57 0.639		46
	Yersinia pestis CO92		fig1214	092.21.peg.156	0	VBIYerPes784	3 1560	YP	21255			FIG01220959: hypothetical protein	0.638		46
12	Yersinia pestis CO92		fig1214	4092.21.peg.875	1	VBIYerPes784	3 0879	YP	0624			Putative membrane protein	0.629		46
	Yersinia pestis CO92		fig1214	092.21.peg.263	0	VBIYerPes784	3 2630	YP	12234		cstA	Carbon starvation protein A paralog	0.624		46
12	Yersinia pestis CO92		fig 214	092.21.peg.401	0	VBIYerPes784	3_4010	YP	13516		mdh	Malate dehydrogenase (EC 1.1.1.37)	0.623		46
10	Yersinia pestis CO92		fig1214	092.21.peg.292	8	V8IYerPes784	3 2928	YP	2511			Uncharacterized conserved protein	0.621		46
	Yersinia pestis CO92		fig 214	092.21.peg.372	2	VBIYerPes784	3_3727	YP	13262			FIG01220564: hypothetical protein	0.619		46
12	Yersinia pestis CO92		fig1214	092.21.peg.372	6	VBIYerPes784	3_3726	YP	13261			Asp-tRNAAsn/Glu-tRNAGin amidotransferase A su	abunit 0.619		46
	Yersinia pestis CO92		fig1214	092.21.peg.415	2	VBIYerPes784	3 4152	YP	13650			Putative metabolite transport protein	0.614		46
	Yersinia pestis CO92		fig1214	092.21.peg.402	4	VBIYerPes784	3 4024	YP	13529		cysQ	3'(2'),5'-bisphosphate nucleotidase (EC 3.1.3.7)	0.611		46
	Yersinia pestis CO92		fig1214	092.21.peg.415	2	VBIYerPes784	3 4150	YP	13648			2-hydroxy-3-oxopropionate reductase (EC 1.1.1.6	50) 0.611		46
10	Yersinia pestis CO92		fig1214	4092.21.peg.248		VBIYerPes784	3 0248	YP	30027			probable haloacid dehalooenase-like hydrolase S	TY3852 0.603		46

17. Notice that the default parameters are set to a correlation cutoff of 0.4, with positive correlation.

Correlation Cutoff:	0.4	~	Correlation:	positive	~	Filter

18. Click on the arrow next to positive and select "negative," then hit filter.

Correlation:	positive	~	Filter
	positive		
	negative		
			1.0.

19. This will show you all the genes that are also negatively correlated with this gene.

_												
ſ	Correlation Cutoff:	0.4 Y Corre	slation: negati	ve 👻	Filter							
146 features found												
Ľ	Workspace	View	Downlo	ad	To	ols		Columns				He
l	Add Feature(s)	FASTA DNA	Table FASTA	. :	MAP IDs to •	Multiple Seq Alignment	6	Show/Hide • Default				🕜 PAT
ľ	8	Genome Name			PATRIC ID	Alt Locus Tag		RefSeq Loo	cus Tag Gene Symb	ol Product Description	Correlation	Cor
Г	E 3	ersinia pestis CO92		fig	214092.21.peg.1197	VBIYerPes7843	197	YPODE	121 pgk	Phosphoglycerate kinase (EC 2.7.2.3)	-0.400	
L	E 1	ersinia pestis CO92		fig	214092.21.peg.4514	VBIYerPes7843	1514	YP039	83	FIG01220178: hypothetical protein	-0.400	
Г	E 3	ersinia pestis CO92		fig	(214092.21.peg.2727	VBIYerPes7843	727	YPO23	122 hrpA	ATP-dependent helicase HrpA	-0.401	
L	E 1	ersinia pestis CO92		fig	(214092.21.peg.4114	VBIYerPes7843	1114	YP036	516	FIG01221499: hypothetical protein	-0.403	
Г	E 3	ersinia pestis CO92		fig	214092.21.peg.1828	VBIYerPes7843	1828	YPO14	198	Putative exported protein precursor	-0.403	
L	E 3	ersinia pestis CO92		ß	1214092.21.peg.912	VBIYerPes7843	912	YPO06	i53 ginE	Glutamate-ammonia-ligase adenylyltransferase (EC 2.7	-0.404	
L	E 3	ersinia pestis CO92		fig	214092.21.peg.1312	VBIYerPes7843	1312	YP010	125 mitA	Membrane-bound lytic murein transglycosylase A precur	-0.404	
L	E 3	ersinia pestis CO92		19	(214092.21.peg.3945	VBIYerPes7843	945	YP034	152	Dipeptide transport ATP-binding protein DppD (TC 3.A.1	-0.405	
г	P1 1	lersinia nestis CO92		60	(214092.21 pep. 1609	VRIVerPerc7843	1609	YP012	199 fn/K	1-phosphofp attrikinase (EC 2.7.1.56)	-0.405	

20. At the bottom of the page, resize the table to show all 146 of the negatively correlated genes.



21. At the top of the table, click on the column header called "RefSeq Locus Tag".

ag	RefSeq Locus Tag 🗢	Gene Symbol	P
0033	YPCD1.26c	уорМ	Т

22. This will sort the results showing the genes in the order they appear in the genome. Look at the results...talk about **AWESOME!** All the members of a Type III Secretion System are correlated, and have similar correlation values. Certain pathogenic bacteria use these structures to inject proteins into the cell that helps the bacteria infect the host.

146 features found										
Workspace Add Feature(s)	View FASTA DNA FASTA Protein	Download Table FASTA	Pathway Summary     MAP IDs to	Multiple Seq Alignment	Columns Show/Hide	- Default			2	
	Genome Name		PATRIC ID	Alt Locus Tag		RefSeq Locus Tag 📥	Gene Symbol	Product Description	Correlation 0	
	Yersinia pestis CO92		fig 214092.21.peg.33	VBIYerPes7843	033	YPCD1.26c	уорМ	Type III secretion possible injected virulence protein (Y	-0.434	
	Yersinia pestis CO92		fig 214092.21.peg.41	VBIYerPes7843	0041	YPCD1.30c	sycD	Type III secretion chaperone protein for YopD (SycD)	-0.462	
	Yersinia pestis CO92		fig 214092.21.peg.42	VBIYerPes7843	0042	YPCD1.31c	lcrV	Type III secretion cytoplasmic LcrG inhibitor (LcrV, secre	-0.422	
	Yersinia pestis CO92		fig 214092.21.peg.46	VBIYerPes7843	0046	YPCD1.35c	yscY	Chaperone protein YscY (Yop proteins translocation prot	-0.454	
	Yersinia pestis CO92		fig 214092.21.peg.56	VBIYerPes7843	0056	YPCD1.45	yscS	Type III secretion inner membrane protein (YscS,homol	-0.592	
	Yersinia pestis CO92		fig 214092.21.peg.57	VBIYerPes7843	0057	YPCD1.46	yscT	Type III secretion inner membrane protein (YscT,HrcT,S	-0.429	
	Yersinia pestis CO92		fig 214092.21.peg.59	VBIYerPes7843	059	YPCD1.49	virF	Type III secretion thermoregulatory protein (LcrF,VirF,tr	-0.580	
	Yersinia pestis CO92		fig 214092.21.peg.60	VBIYerPes7843	0060	YPCD1.51	yscB	Type III secretion chaperone protein for YopN (SycN,Ys	-0.435	
	Yersinia pestis CO92		fig 214092.21.peg.63	VBIYerPes7843	0063	YPCD1.53	yscD	Type III secretion inner membrane protein (YscD,homol	-0.495	
	Yersinia pestis CO92		fig 214092.21.peg.64	VBIYerPes7843	0064	YPCD1.54	yscE	Type III secretion protein (YscE)	-0.567	
	Yersinia pestis CO92		fig 214092.21.peg.65	VBIYerPes7843	0065	YPCD1.55	yscF	Type III secretion cytoplasmic protein (YscF)	-0.417	
	Yersinia pestis CO92		fig 214092.21.peg.68	VBIYerPes7843	0068	YPCD1.58	lcrO	Type III secretion cytoplasmic protein (YscI)	-0.423	
	Yersinia pestis CO92		fig 214092.21.peg.69	VBIYerPes7843	0069	YPCD1.59	ylpB	Type III secretion bridge between inner and outermem	-0.472	
	Yersinia pestis CO92		fig 214092.21.peg.70	VBIYerPes7843	0070	YPCD1.60	yscK	Type III secretion cytoplasmic protein (YscK)	-0.486	
	Yersinia pestis CO92		fig 214092.21.peg.71	VBIYerPes7843	0071	YPCD1.61	yscL	Type III secretion cytoplasmic protein (YscL)	-0.562	
	Yersinia pestis CO92		fig 214092.21.peg.72	VBIYerPes7843	072	YPCD1.62	lcrQ	Type III secretion negative regulator of effector product	-0.486	

Just for fun...here's a picture of what they think the Type III secretion system looks like and how the proteins line up.



And here's a transmission electron microscope image of one a Type III secretion system from *Salmonella*. You can clearly see the needle-like apparatus that they use to inject proteins into the host cell.



## Assignment: Answer the following questions using the PATRIC website.

- 1. Choose one of the Type III Secretion System genes and get to the landing page for it. Open the Correlation Tab.
  - a. Look at the genes that are positively correlated with the gene you chose. Adjust the correlation cut-off (located above the table) to narrow the number of genes you see.
  - b. Which genes are the most strongly correlated?
- 2. Go to your workspace and select other genes from the group you created Part II, Number 6. Examine the positively and negatively correlated genes for several of them. Are there any pathways that these correlated genes share?
- 3. Follow the same protocol above, but in this case select the 37°C condition as the one that is up-regulated, and the 26°C condition as the one that is down-regulated. Set the log ratio to 1 and filter. Then follow all the steps listed above, and chose one specific gene to drill down on.
  - a. How many genes are significantly up-regulated at that specific logratio when you choose those conditions.
  - b. How many pathways do the genes appear in?
  - c. What gene(s) did you choose to examine?
    - i. What log ratio did you filter on to examine this gene, and what experimental conditions surfaced when you changed that?
    - ii. When you did the positive and negative correlation, did you see any genes of interest (Hint: The flagellar genes looked interesting to me)?
  - d. Bonus question: We haven't discussed this, but look at the tabs across the gene landing page. How would you look at the gene you chose and its gene neighborhood (the genes around it)? Which tab did you choose and what did you see?

#### References

- 1. Raoult, D., et al., *Plague: history and contemporary analysis.* J Infect, 2013. **66**(1): p. 18-26.
- 2. Butler, T., *Plague history: Yersin's discovery of the causative bacterium in 1894 enabled, in the subsequent century, scientific progress in understanding the disease and the development of treatments and vaccines.* Clin Microbiol Infect, 2014. **20**(3): p. 202-9.
- 3. Galindo, C.L., et al., *Comparative Global Gene Expression Profiles of Wild-Type Yersinia pestis CO92 and Its Braun Lipoprotein Mutant at Flea and Human Body Temperatures.* Comp Funct Genomics, 2010: p. 342168.