Yersin, A. La Peste Bubonique A Hong-Kong. In *Annales de l'Institut Pasteur (Journal De Microbiologie)*; Paris : Masson, 1894; Vol. 8, pp 662–667.

This paper identifies the causative bacteria of the Bubonic Plague.
https://www.biodiversitylibrary.org/item/23590

1894

1950

1954

Englesberg, E.; Levy, J. B.; Gibor, A. Some Enzymatic Changes Accompanying The Shift From Anaerobiosis To Aerobiosis In Pasteurella Pestis. *J Bacteriol* **1954**, *68* (2), 178–185.

Cells grown in aerobic and anaerobic conditions have different enzymatic activity. Aerobic cells have greater concentrations of triphosphopyridine nucleotide-linked isocitric dehydrogenase, aconitase, fumarase, and cytochrome.

1956

Davies, D. A. L. A Specific Polysaccharide of Pasteurella Pestis. *Biochem J* **1956**, *63* (1), 105–116.

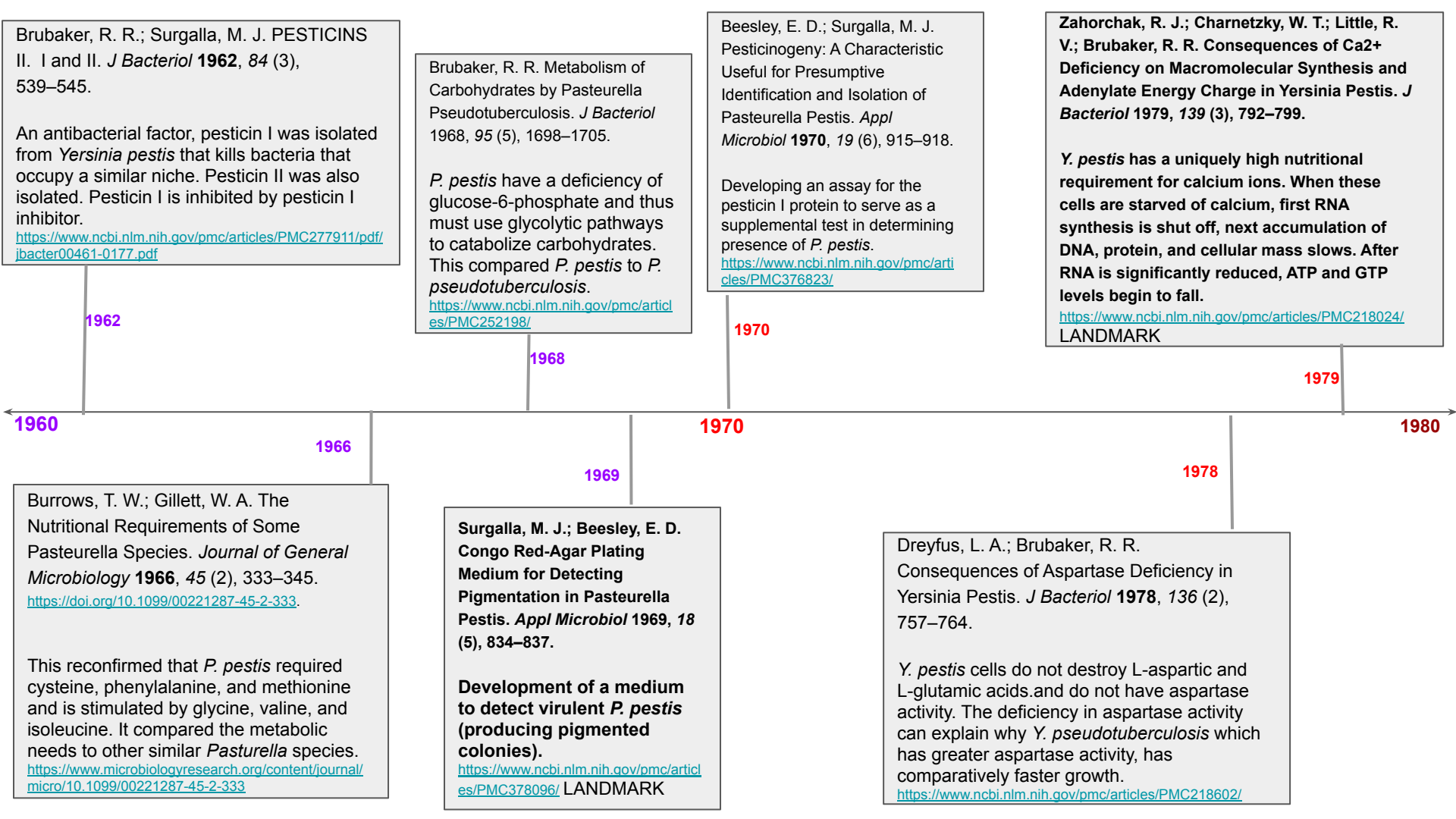
A lipopolysaccharide wa extracted and purified from *Yersinia Pestis*. The lipopolysaccharide has glucose, glucosamine, and an unidentified sugar. It is not protective or toxic.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1216007/

1959

Higuchi, K.; Kupferberg, L. L.; Smith, J. L. Studies On The Nutrition And Physiology Of Pasteurella Pestis. *J Bacteriol* 1959, *77* (3), 317–321.

The calcium ion concentrations required by *Yersinia pestis* [in older literature called *Pasteurella pestis*] are approximately equivalent to concentration of calcium in human serum. The role of calcium is still unknown
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC290369/pdf/jbacter00500-0085.pdf
LANDMARK

1960


Brubaker, R. R.; Surgalla, M. J. PESTICINS II. I and II. *J Bacteriol* **1962**, *84* (3), 539–545.
An antibacterial factor, pesticin I was isolated from *Yersinia pestis* that kills bacteria that occupy a similar niche. Pesticin II was also isolated. Pesticin I is inhibited by pesticin I inhibitor.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC277911/pdf/jbacter00461-0177.pdf
1962
Brubaker, R. R. Metabolism of Carbohydrates by Pasteurella Pseudotuberculosis. *J Bacteriol* 1968, *95* (5), 1698–1705.
P. pestis have a deficiency of glucose-6-phosphate and thus must use glycolytic pathways to catabolize carbohydrates. This compared *P. pestis* to *P. pseudotuberculosis*.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC252198/
1968
Beesley, E. D.; Surgalla, M. J. Pesticinogeny: A Characteristic Useful for Presumptive Identification and Isolation of Pasteurella Pestis. *Appl Microbiol* **1970**, *19* (6), 915–918.
Developing an assay for the pesticin I protein to serve as a supplemental test in determining presence of *P. pestis*.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC376823/
1970
Zahorchak, R. J.; Charnetzky, W. T.; Little, R. V.; Brubaker, R. R. Consequences of Ca2+ Deficiency on Macromolecular Synthesis and Adenylate Energy Charge in Yersinia Pestis. *J Bacteriol* 1979, *139* (3), 792–799.
***Y. pestis* has a uniquely high nutritional requirement for calcium ions. When these cells are starved of calcium, first RNA synthesis is shut off, next accumulation of DNA, protein, and cellular mass slows. After RNA is significantly reduced, ATP and GTP levels begin to fall.**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC218024/
LANDMARK
1979
1960
1966
1969
1978
1980
Burrows, T. W.; Gillett, W. A. The Nutritional Requirements of Some Pasteurella Species. *Journal of General Microbiology* **1966**, *45* (2), 333–345.
https://doi.org/10.1099/00221287-45-2-333.
This reconfirmed that *P. pestis* required cysteine, phenylalanine, and methionine and is stimulated by glycine, valine, and isoleucine. It compared the metabolic needs to other similar *Pasturella* species.
https://www.microbiologyresearch.org/content/journal/micro/10.1099/00221287-45-2-333
Surgalla, M. J.; Beesley, E. D. Congo Red-Agar Plating Medium for Detecting Pigmentation in Pasteurella Pestis. *Appl Microbiol* 1969, *18* (5), 834–837.
Development of a medium to detect virulent *P. pestis* (producing pigmented colonies).
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC378096/ LANDMARK
Dreyfus, L. A.; Brubaker, R. R. Consequences of Aspartase Deficiency in Yersinia Pestis. *J Bacteriol* **1978**, *136* (2), 757–764.
Y. pestis cells do not destroy L-aspartic and L-glutamic acids.and do not have aspartase activity. The deficiency in aspartase activity can explain why *Y. pseudotuberculosis* which has greater aspartase activity, has comparatively faster growth.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC218602/

1980

1981

Hillier, S.; Charnetzky, W. T. Glyoxylate Bypass Enzymes in Yersinia Species and Multiple Forms of Isocitrate Lyase in Yersinia Pestis. *J Bacteriol* **1981**, *145* (1), 452–458.

Y. pestis likely expresses two forms of isocitrate lyase that are expressed in response to the sugar input of it's diet. One form functions for an acetate diet and the other for a xylose diet. On a xylose diet,growth is not easily inhibited.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC217293/pdf/jbacter00272-0472.pdf LANDMARK

1982

Charnetzky, W. T.; Brubaker, R. R. RNA Synthesis in Yersinia Pestis During Growth Restriction in Calcium-Deficient Medium. *J Bacteriol* **1982**, *149* (3), 1089–1095.

Y. pestis cells require 2.5mM concentrations of the calcium ion at human temperature (37C) and less calcium at the lower temperature 26C at which it can also grow. In calcium-deficient medium, the 37C cell is viable, but not growing. RNA synthesis is decreased and shifts focus to majority mRNA production.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC216499/

1988

Sodeinde, O. A.; Sample, A. K.; Brubaker, R. R.; Goguen, J. D. Plasminogen Activator/Coagulase Gene of Yersinia Pestis Is Responsible for Degradation of Plasmid-Encoded Outer Membrane Proteins. *Infect Immun* **1988**, *56* (10), 2749–2752.

Y. pestis typically have a plasmid that degrades Yersinia outer membrane proteins (YOP) typical to the genus. YOP are degraded because of a plasmid specific to *Y. Pestis*; specifically by mutations in the pla gene which allows for plasminogen activator and coagulase activase.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC259639/

1990

1992

Sodeinde, O. A.; Subrahmanyam, Y. V. B. K. Stark, K.; Quan, T.; Bao, Y.; Goguen, J. D. A Surface Protease and the Invasive Character of Plague. *Science* 1992, *258* (5084), 1004–1007.

The smaller 9.5kb plasmid of *Y. pestis*'s two plasmids contributes greatly to the lethality of plague. The plasmid produces pesticin (pst gene) and a pla protein that confers immunity for pesticin (pla gene) by lysis of fibrin clots by plasminogen activation. Pla encodes a surface protease and allows the bacteria to infect deep tissue.

https://www.jstor.org/stable/2881682 LANDMARK

1993

Hoe, N. P.; Goguen, J. D. Temperature Sensing in Yersinia Pestis: Translation of the LcrF Activator Protein Is Thermally Regulated. *J Bacteriol* 1993, *175* (24), 7901–7909.

At 26C and 37C transcription rates of the lcrF gene, which encodes for a transcription activator that induces virulence-reated proteins, are similar. However, the efficiency of translation increases with temperature since a stem-loop containing the Shine-Dalgarno sequence is unstable at 37C and thus allows the sequence to be read. LANDMARK

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC206968/

1996

Hinnebusch, B. J.; Perry, R. D.; Schwan, T. G. Role of the Yersinia Pestis Hemin Storage (Hms) Locus in the Transmission of Plague by Fleas. *Science* **1996**, *273* (5273), 367–370. https://doi.org/10.1126/science.273.5273.367.

Plague transmission requires a locus of plague bacilli to "block" the gut of the infected flea, causing the flea to regurgitate *Y. pestis* into the bite site. The hemin storage locus (hms), which contains outer membrane proteins (hmsF and hmsH) and hmsR of *Y. pestis* is needed to form the blockage.

https://www.science.org/doi/10.1126/science.273.5273.367 LANDMARK

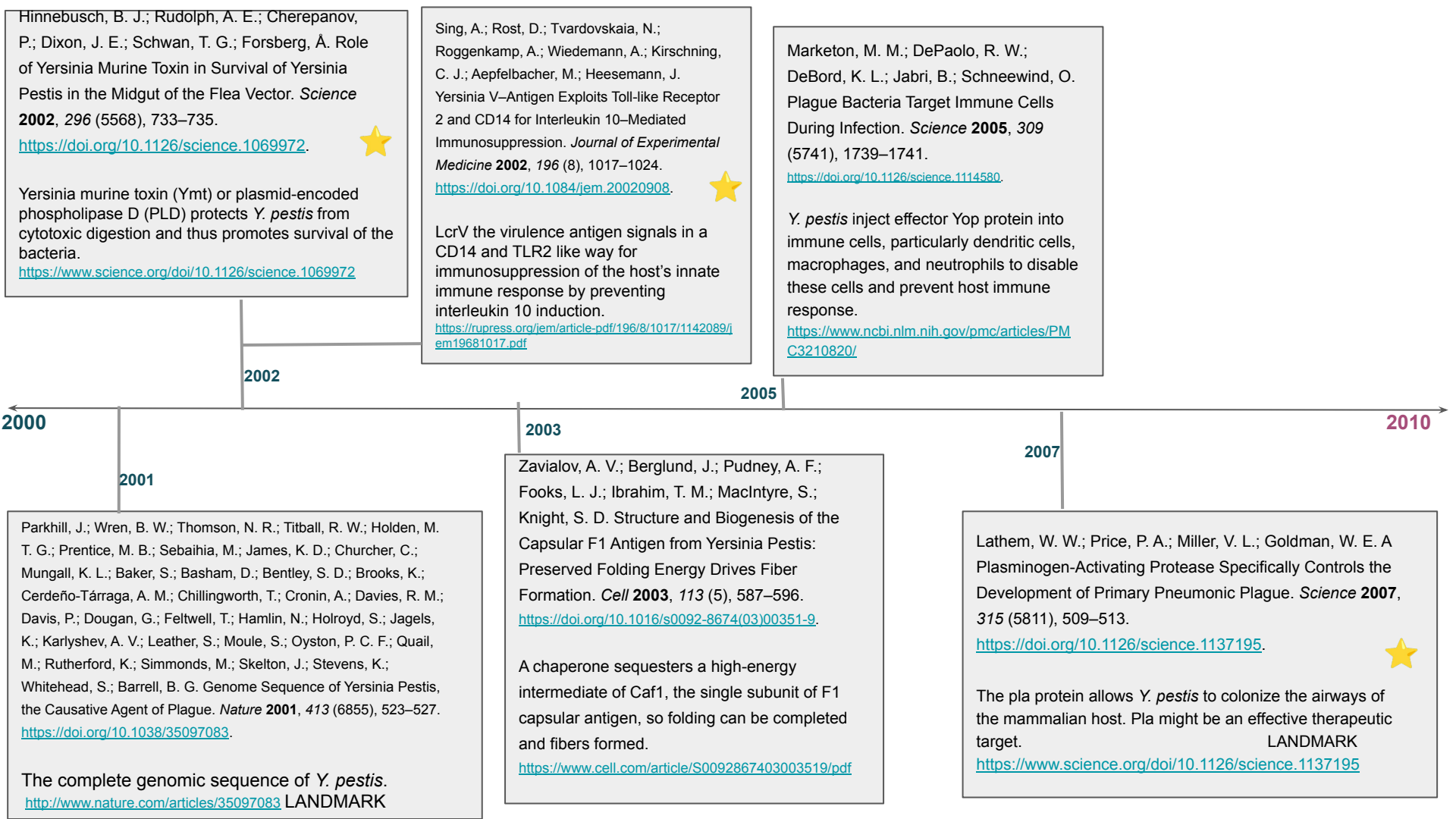
1999

Bearden, S. W.; Perry, R. D. The Yfe System of Yersinia Pestis Transports Iron and Manganese and Is Required for Full Virulence of Plague. *Mol Microbiol* **1999**, *32* (2), 403–414. https://doi.org/10.1046/j.1365-2958.1999.01360.x.

The Yfe locus has two operons, the yfeABCD encodes a transport system for iron and manganese. The transport system is more active in the virulent (pigmented) *Y. pestis*.

https://onlinelibrary.wiley.com/doi/full/10.1046/j.1365-2958.1999.01360.x?sid=nlm%3Apubmed#

2000


Hinnebusch, B. J.; Rudolph, A. E.; Cherepanov, P.; Dixon, J. E.; Schwan, T. G.; Forsberg, Å. Role of Yersinia Murine Toxin in Survival of Yersinia Pestis in the Midgut of the Flea Vector. *Science* **2002**, *296* (5568), 733–735. https://doi.org/10.1126/science.1069972.
Yersinia murine toxin (Ymt) or plasmid-encoded phospholipase D (PLD) protects *Y. pestis* from cytotoxic digestion and thus promotes survival of the bacteria.
https://www.science.org/doi/10.1126/science.1069972
Sing, A.; Rost, D.; Tvardovskaia, N.; Roggenkamp, A.; Wiedemann, A.; Kirschning, C. J.; Aepfelbacher, M.; Heesemann, J. Yersinia V–Antigen Exploits Toll-like Receptor 2 and CD14 for Interleukin 10–Mediated Immunosuppression. *Journal of Experimental Medicine* **2002**, *196* (8), 1017–1024. https://doi.org/10.1084/jem.20020908.
LcrV the virulence antigen signals in a CD14 and TLR2 like way for immunosuppression of the host's innate immune response by preventing interleukin 10 induction.
https://rupress.org/jem/article-pdf/196/8/1017/1142089/jem19681017.pdf
Marketon, M. M.; DePaolo, R. W.; DeBord, K. L.; Jabri, B.; Schneewind, O. Plague Bacteria Target Immune Cells During Infection. *Science* **2005**, *309* (5741), 1739–1741. https://doi.org/10.1126/science.1114580.
Y. pestis inject effector Yop protein into immune cells, particularly dendritic cells, macrophages, and neutrophils to disable these cells and prevent host immune response.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3210820/
2000
2001
2002
2003
2005
2007
2010
Parkhill, J.; Wren, B. W.; Thomson, N. R.; Titball, R. W.; Holden, M. T. G.; Prentice, M. B.; Sebaihia, M.; James, K. D.; Churcher, C.; Mungall, K. L.; Baker, S.; Basham, D.; Bentley, S. D.; Brooks, K.; Cerdeño-Tárraga, A. M.; Chillingworth, T.; Cronin, A.; Davies, R. M.; Davis, P.; Dougan, G.; Feltwell, T.; Hamlin, N.; Holroyd, S.; Jagels, K.; Karlyshev, A. V.; Leather, S.; Moule, S.; Oyston, P. C. F.; Quail, M.; Rutherford, K.; Simmonds, M.; Skelton, J.; Stevens, K.; Whitehead, S.; Barrell, B. G. Genome Sequence of Yersinia Pestis, the Causative Agent of Plague. *Nature* **2001**, *413* (6855), 523–527. https://doi.org/10.1038/35097083.
The complete genomic sequence of *Y. pestis*.
http://www.nature.com/articles/35097083 LANDMARK
Zavialov, A. V.; Berglund, J.; Pudney, A. F.; Fooks, L. J.; Ibrahim, T. M.; MacIntyre, S.; Knight, S. D. Structure and Biogenesis of the Capsular F1 Antigen from Yersinia Pestis: Preserved Folding Energy Drives Fiber Formation. *Cell* **2003**, *113* (5), 587–596. https://doi.org/10.1016/s0092-8674(03)00351-9.
A chaperone sequesters a high-energy intermediate of Caf1, the single subunit of F1 capsular antigen, so folding can be completed and fibers formed.
https://www.cell.com/article/S0092867403003519/pdf
Lathem, W. W.; Price, P. A.; Miller, V. L.; Goldman, W. E. A Plasminogen-Activating Protease Specifically Controls the Development of Primary Pneumonic Plague. *Science* **2007**, *315* (5811), 509–513. https://doi.org/10.1126/science.1137195.
The pla protein allows *Y. pestis* to colonize the airways of the mammalian host. Pla might be an effective therapeutic target. LANDMARK
https://www.science.org/doi/10.1126/science.1137195

2010

2011

Bobrov, A. G.; Kirillina, O.; Ryjenkov, D. A.; Waters, C. M.; Price, P. A.; Fetherston, J. D.; Mack, D.; Goldman, W. E.; Gomelsky, M.; Perry, R. D. Systematic Analysis of Cyclic Di-GMP Signalling Enzymes and Their Role in Biofilm Formation and Virulence in Yersinia Pestis. *Mol Microbiol* **2011**, *79* (2), 533–551. https://doi.org/10.1111/j.1365-2958.2010.07470.x.

The genes hmsT, hmsP, and y370 encode enzymes capable of synthesizing cyclic-di-GMP, which is the signaling molecule that helps to inversely regulate biofilm formation. The c-di-GMP signaling pathway is not essential for virulence and if knocked out, more favorable pathways will emerge.

2012

Vladimer, G. I.; Weng, D.; Paquette, S. W. M.; Vanaja, S. K.; Rathinam, V. A. K.; Aune, M. H.; Conlon, J. E.; Burbage, J. J.; Proulx, M. K.; Liu, Q.; Reed, G.; Mecsas, J. C.; Iwakura, Y.; Bertin, J.; Goguen, J. D.; Fitzgerald, K. A.; Lien, E. The NLRP12 Inflammasome Recognizes Yersinia Pestis. *Immunity* **2012**, *37* (1), 96–107. https://doi.org/10.1016/j.immuni.2012.07.006.

Y. pestis suppresses IL-18 and 1L-1B inflammatory cytokines through NLRP12 inflammasome activation.

2013

Arthur, J. S. C.; Ley, S. C. Mitogen-Activated Protein Kinases in Innate Immunity. *Nature Reviews Immunology* **2013**, *13* (9), 679–692. https://doi.org/10.1038/nri3495.

Y. pestis uses type 3 secretion systems to interfere with intracellular signaling in host cells. YopJ acetylates residues in MKKs, IKK1 and IKK2 which blocks the activation of MAPKs and proteolysis of IkBs thus allowing NF-kB signaling

https://search.ebscohost.com/login.aspx?direct=true&db=a9h&AN=89926347&site=eds-live

2017

Mitchell, A.; Tam, C.; Elli, D.; Charlton, T.; Osei-Owusu, P.; Fazlollahi, F.; Faull, K. F.; Schneewind, O. Glutathionylation of Yersinia Pestis LcrV and Its Effects on Plague Pathogenesis. *mBio* **2017**, *8* (3), e00646-17. https://doi.org/10.1128/mBio.00646-17.

The cap protein of type 3 secretion needle, LcrV is glutathionylated. This glutathionylation contributes to plague pathogenesis.

2019

Qasem-Abdullah, H.; Perach, M.; Livnat-Levanon, N.; Lewinson, O. ATP Binding and Hydrolysis Disrupt the High-Affinity Interaction between the Heme ABC Transporter HmuUV and Its Cognate Substrate-Binding Protein. *J Biol Chem* **2017**, *292* (35), 14617–14624. https://doi.org/10.1074/jbc.M117.779975.

The ABC heme importer (HmuUV) binding to its substrate (HmuT) is reduced by excess HmuT presence and completely inhibited by ATP presence. Presents ATP hydrolysis mechanism that allows for the importer to function.

Osei-Owusu, P.; Charlton, T. M.; Kim, H. K.; Missiakas, D.; Schneewind, O. FPR1 Is the Plague Receptor on Host Immune Cells. *Nature* **2019**, *574* (7776), 57–62. https://doi.org/10.1038/s41586-019-1570-z.

LcrV binds to N-formylpeptide receptor (FPR1) to promote the translocation of effects. The receptor is present in mice and humans; it's absence provides protection against the bacteria.
LANDMARK

2020

Bland, D. M.; Miarinjara, A.; Bosio, C. F.; Calarco, J.; Hinnebusch, B. J. Acquisition of Yersinia Murine Toxin Enabled Yersinia Pestis to Expand the Range of Mammalian Hosts That Sustain Flea-Borne Plague. *PLoS Pathog* **2021**, *17* (10), e1009995. https://doi.org/10.1371/journal.ppat.1009995.

Yersinia murine toxin (Ymt) allows for bacterial survival in the flea gut by digesting red blood cells. Without this phospholipase enzyme, the bacteria could not survive in mammalian hosts.

Quinn, J. D.; Weening, E. H.; Miller, V. L. PsaF Is a Membrane-Localized PH Sensor That Regulates PsaA Expression in Yersinia Pestis. *J Bacteriol* **2021**, *203* (16), e0016521. https://doi.org/10.1128/JB.00165-21.

Regulatory proteins PsaE and PsaF are reduced at neutral pH and present at mildly acidic pH. At neutral pH, the pH 6 antigen (PsaA) which forms fimbria structures necessary for virulence is mildly expressed. PsaF acts as a pH sensor and enhances the stability of PsaE. PsaF is regulated by PH and regulated PsaE, which regulates PsaA.
https://journals.asm.org/doi/pdf/10.1128/JB.00165-21

2020 **2021** **2022**

Cao, S.; Chen, Y.; Yan, Y.; Zhu, S.; Tan, Y.; Wang, T.; Song, Y.; Deng, H.; Yang, R.; Du, Z. Secretome and Comparative Proteomics of Yersinia Pestis Identify Two Novel E3 Ubiquitin Ligases That Contribute to Plague Virulence. *Mol Cell Proteomics* **2021**, *20*, 100066. https://doi.org/10.1016/j.mcpro.2021.100066.

In mammalian hosts, certain membrane proteins, chaperonins, and stress response proteins are upregulated compared to the levels of the proteins expressed in the flea vector. YP_3416 and YP_3418 have E3 ubiquitin ligase activity.