Fujian Agriculture and Forestry University 福建农林大学

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Resistenz gegen Schwermetalle und Interaktion mit Antibiotika-Resistenzen

Christopher Rensing PhD

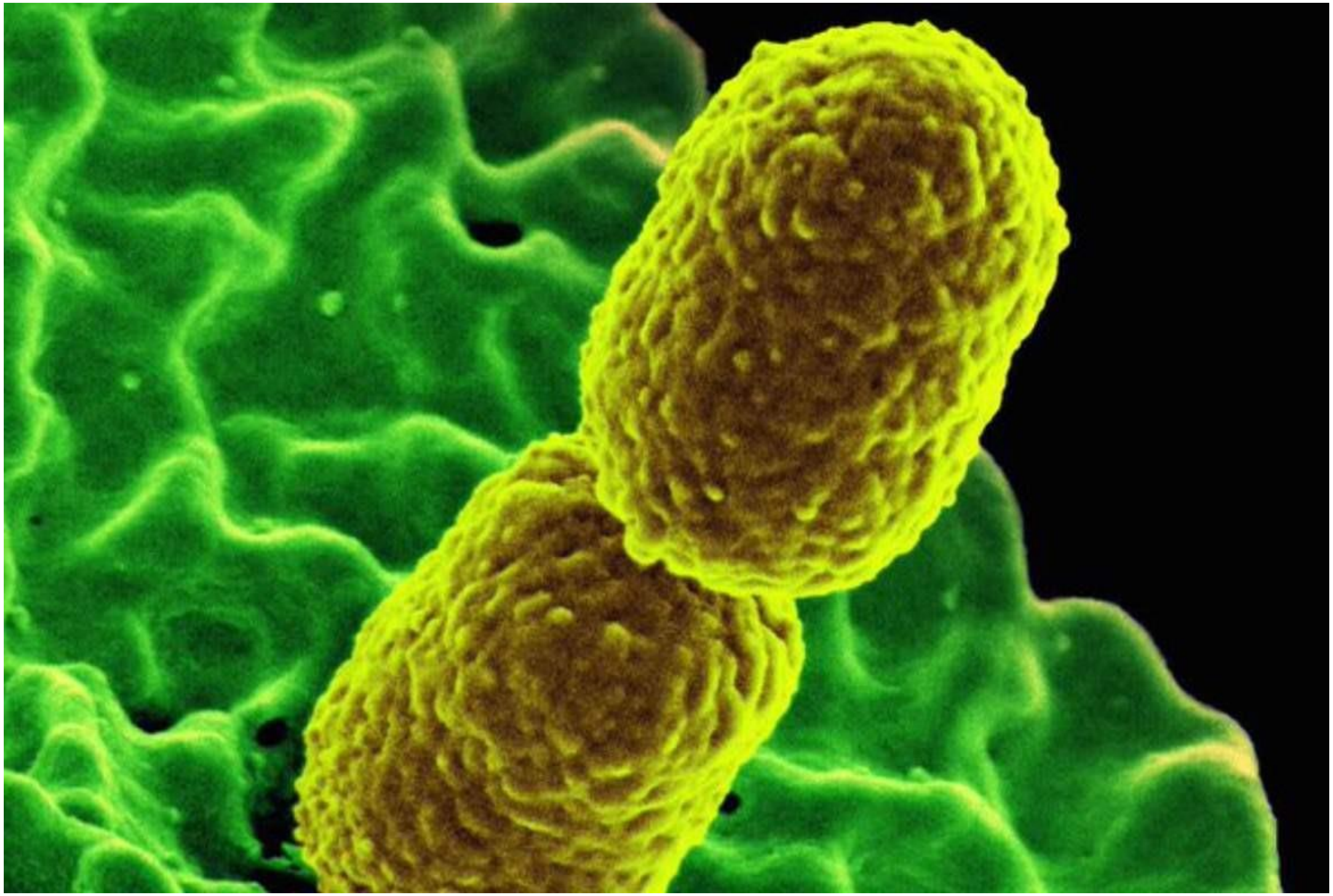
Fujian Agriculture & Forestry University

Fuzhou

Fujian Provincial Hospital

Team

Klebsiella pneumonia

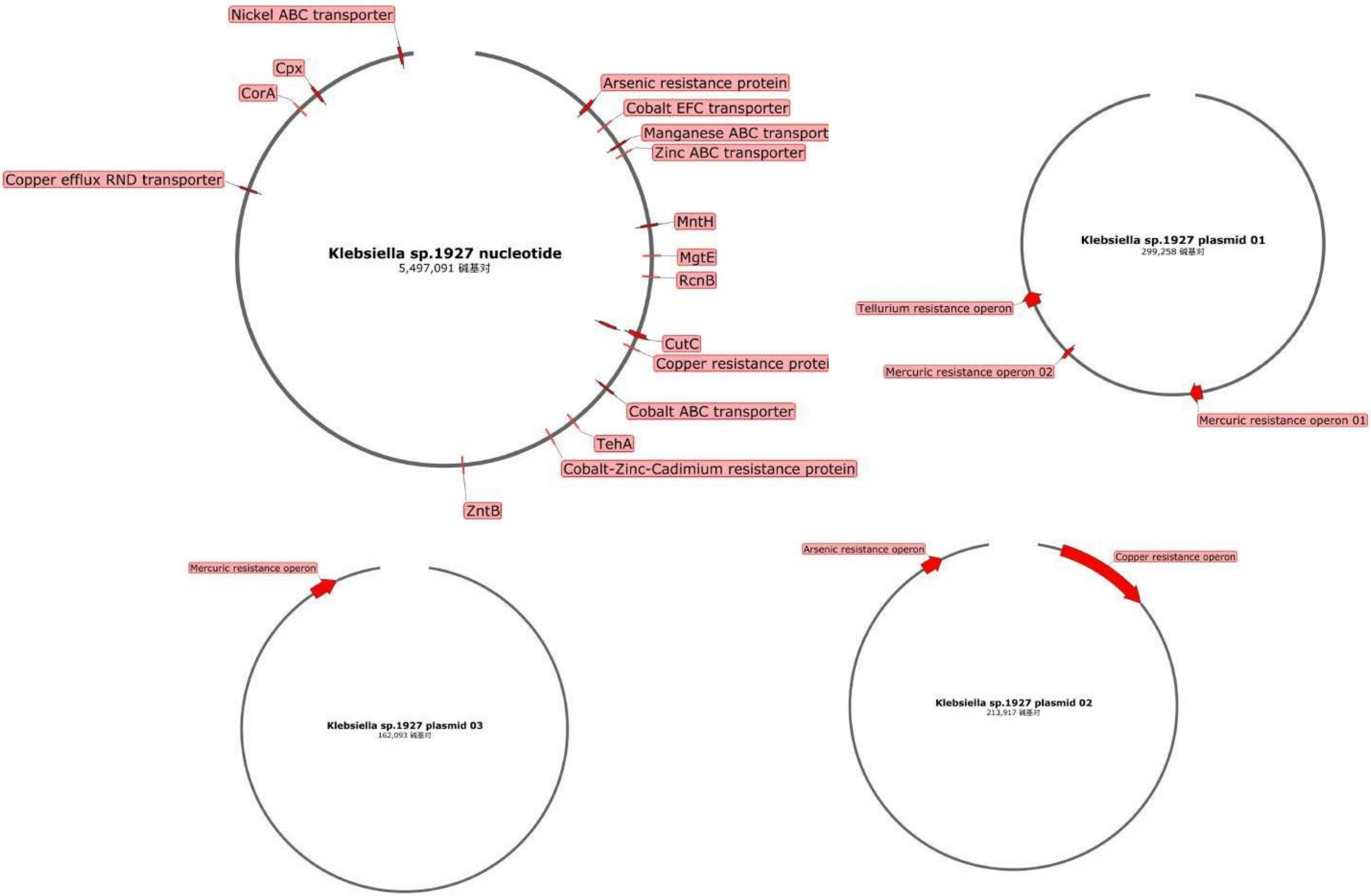


The MIC of 1927 and 1954

	1927	**1954**
Amp(ppm)	>30,000	>30,000
Km(ppm)	13,000	14,000
Cm(ppm)	2,000	4,000
Gm(ppm)	6,000	7,000
Tet(ppm)	250	250
Rif(ppm)	10	15
Str(ppm)	40	10
Au(μmol/L)	900	<400
Cu(mmol/L)	2	0.25
Ag(μmol/L)	128	>1024
Cd(mmol/L)	7	5
As (III) (mmol/L)	12.5	0.5

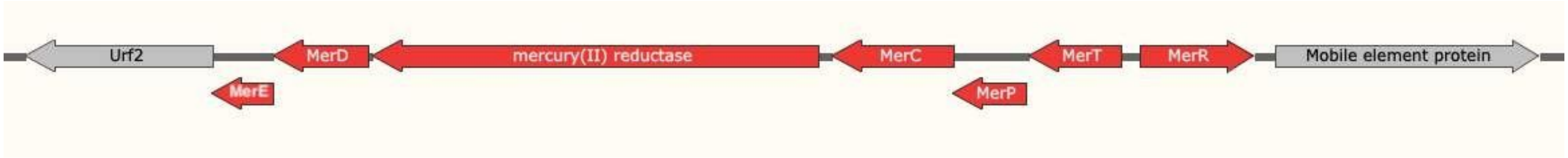
1927 isolated from sputum of a patient with pneumonia.
1954 isolated from sputum of a patient with hydrocephalus.

Klebsiella sp.1927 Gene Map

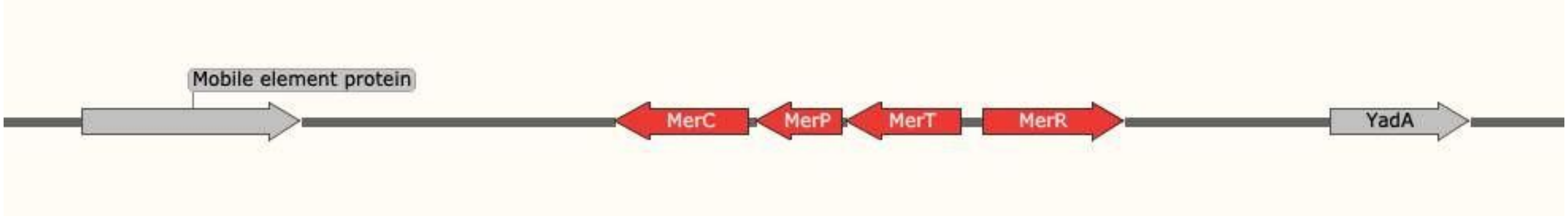


Heavy metal resistance genes(cluster) in *Klebsiella* sp.1927 plasmid 01

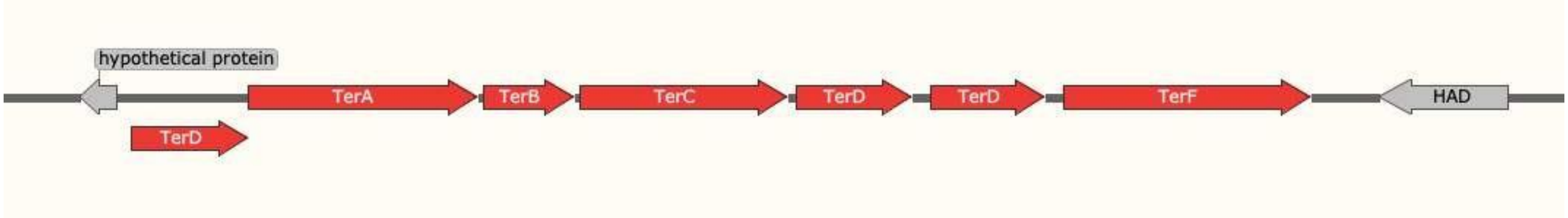
Mercuric resistance operon 01



Mercuric resistance operon 02

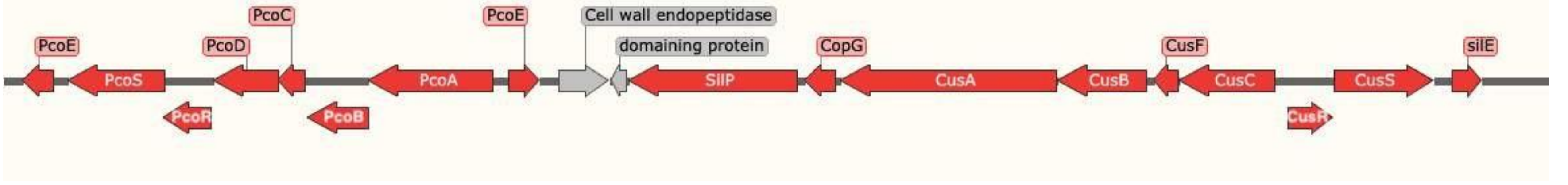


Tellurium resistance operon

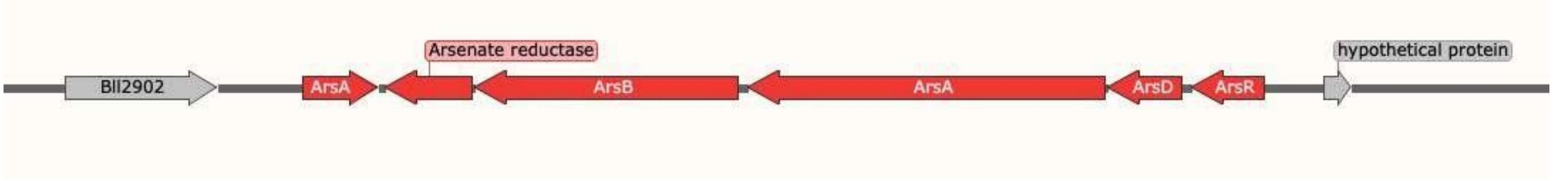


Heavy metal resistance genes(cluster) in *Klebsiella* sp.1927 plasmid 02

Copper resistance operon

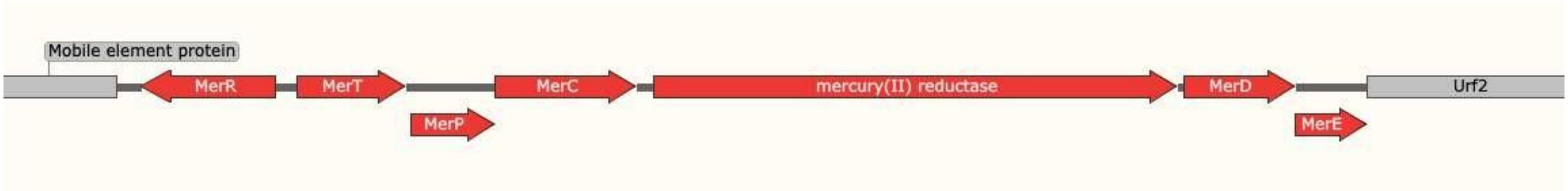


Arsenic resistance operon



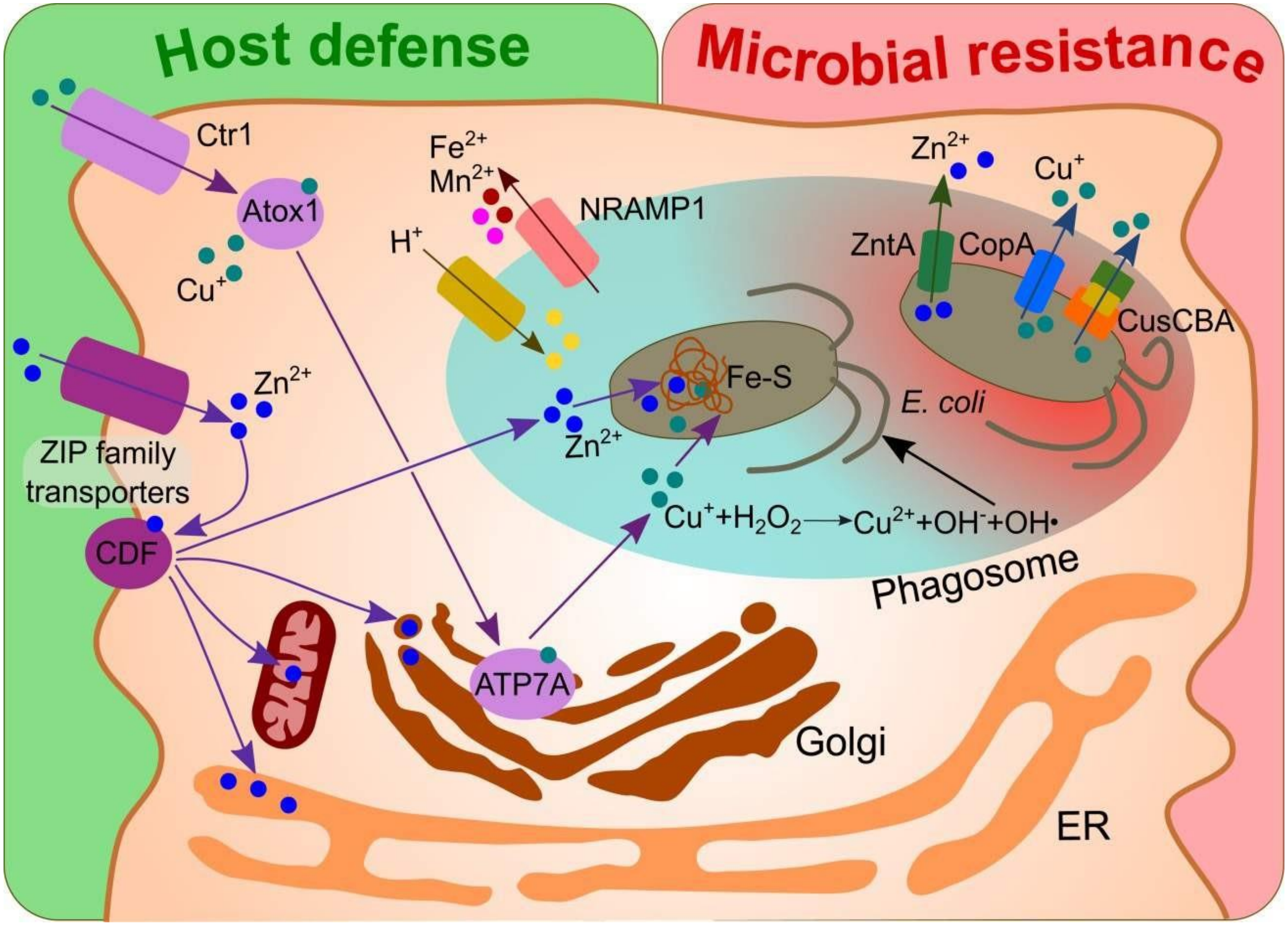
Heavy metal resistance genes(cluster) in *Klebsiella* sp.1927 plasmid 03

Mercuric resistance operon

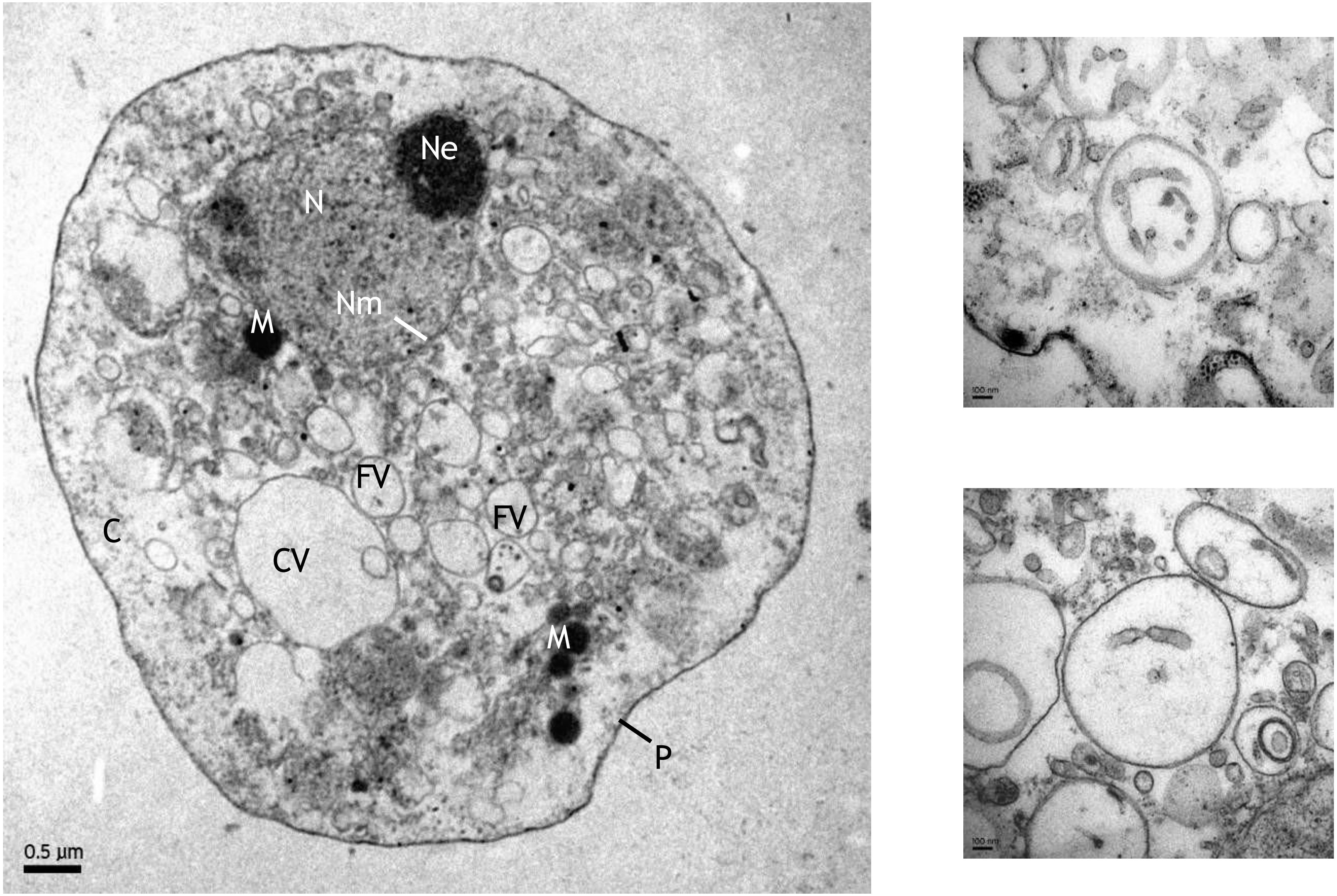


- Warum?
- 3 *mer* operons
- Tellurium operon
- 19 Gen Kupfer Resistenz cluster
- Extra *ars* operon

Bacterial killing in macrophage/amoeba



Hao et al., Appl Microbiol Biotechnol (2015)



Ne: nucleolus; **N**: nucleus; **Nm**: nucleus membrane; **M**: mitochondrion;
V: Food vacuole; **CV**: contractile vacuole; **C**: Cytoplasm; **P**: Plasma membrane

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Bacterial killing in macrophages and amoeba: do they all use a brass dagger?

Nadezhda German[1], Dominik Doyscher[2] & Christopher Rensing*[3]
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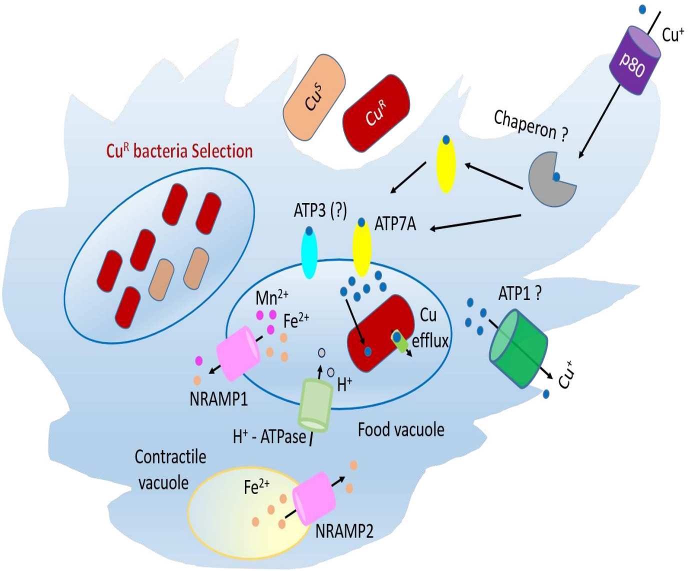
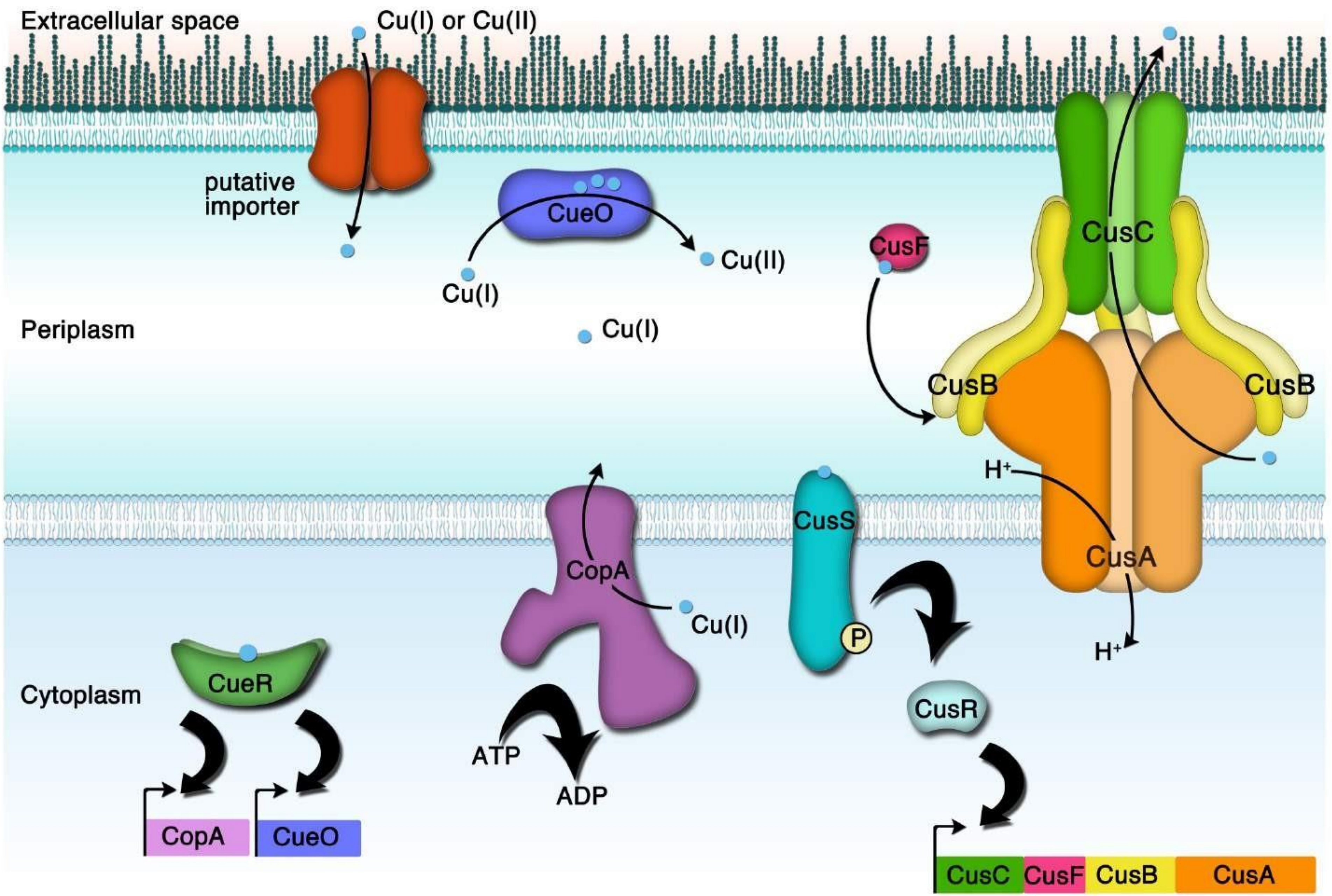
[2]Department of Veterinary Sciences, Ludwig-Maximilians-University Munich, Oberschlessheim, Germany
[3]Department of Plant & Environmental Sciences, University of Copenhagen, Frederiksberg, Denmark
*Author for correspondence: chres@life.ku.dk



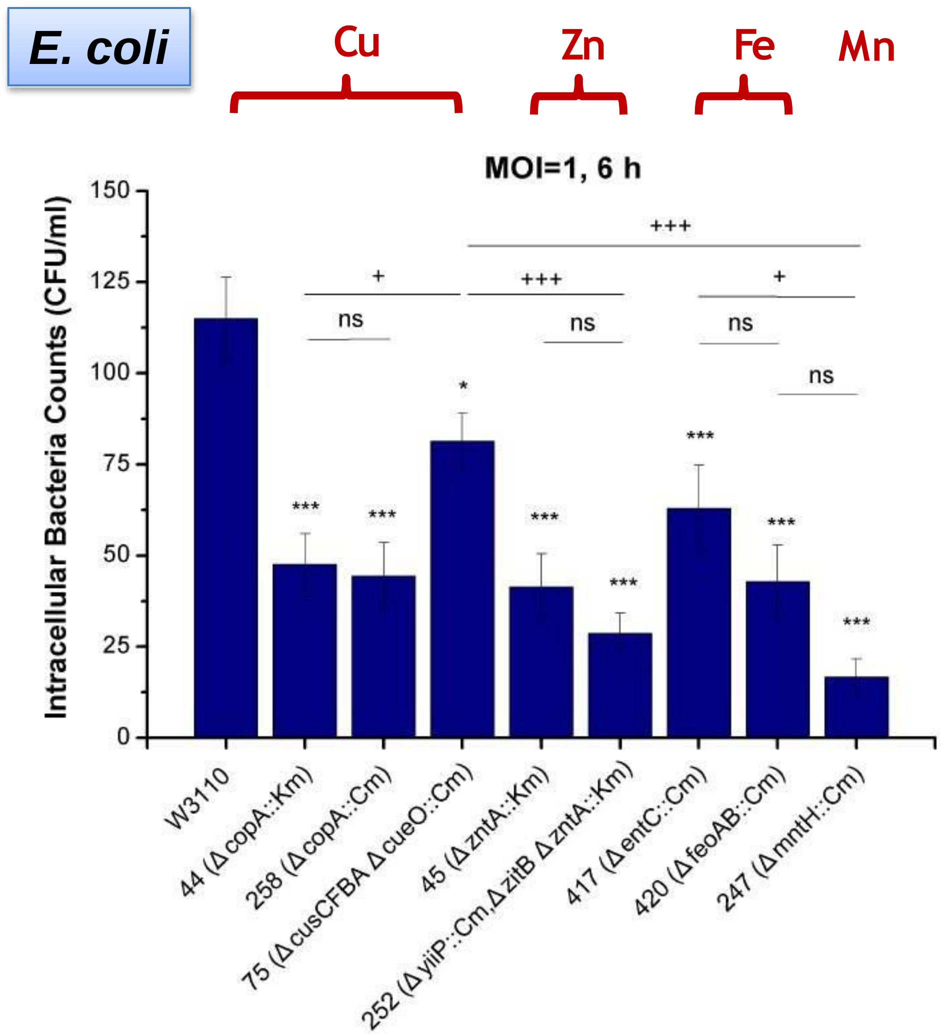
Conclusions

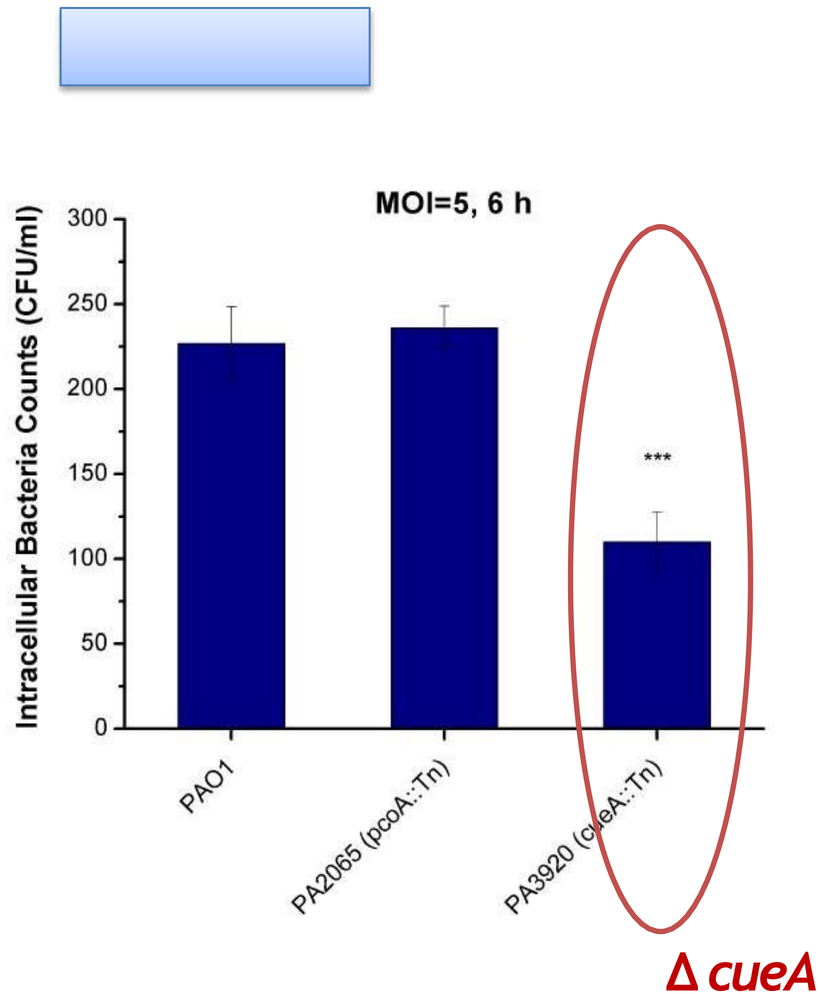
This review presents a now considerable body of data consistent with the hypothesis that Cu and Zn toxicity can contribute to the clearance of bacterial pathogens. This has led to the intriguing concept of the "brass dagger" in innate immunity (30), which then raises the question of how such a bactericidal mechanism could be integrated into the complex immune sys-



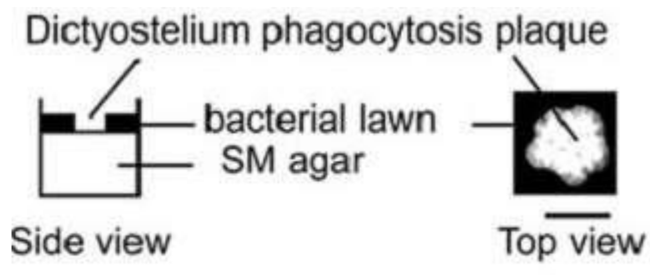
Extracellular space
Cu(I) or Cu(II)
putative importer
CueO
Cu(I)
Cu(II)
Periplasm
Cu(I)
CusF
CusC
CusB
CusB
CusA
H+
H+
CusS
P
CusR
CopA
Cu(I)
ATP
ADP
CueR
Cytoplasm
CopA
CueO
CusC
CusF
CusB
CusA

Cu/Zn exporters and Fe/Mn uptake systems are essential for bacterial survival in *Dictyostelium*



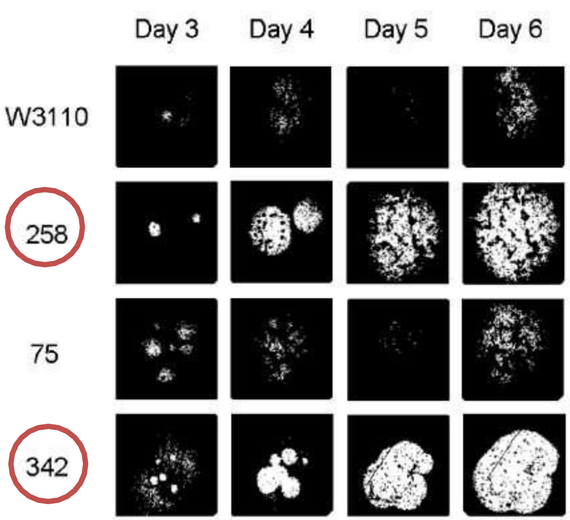


Survival with different copper resistance determinants towards *Dictyostelium*



Alibaud *et al*. Cellular Microbiology,

E. coli, 2.5% HL5-agar

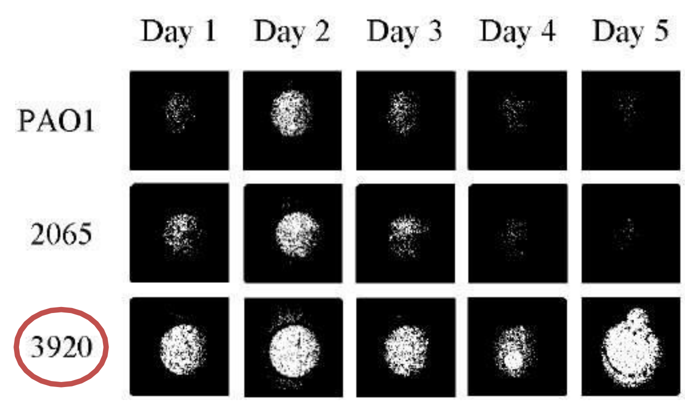


E.coli 258: Δ*copA*::Cm

E.coli 75: Δ*cusCFBA*, Δ*cueO*::Cm

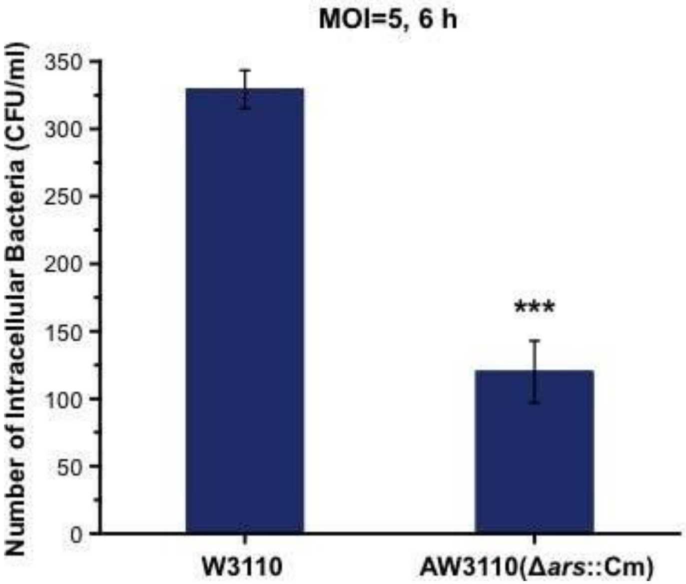
E.coli 342: Δ*copA*::Km, Δ*cusCFBA*, Δ*cueO*::Cm

Pseudomonas , 5% HL5-agar



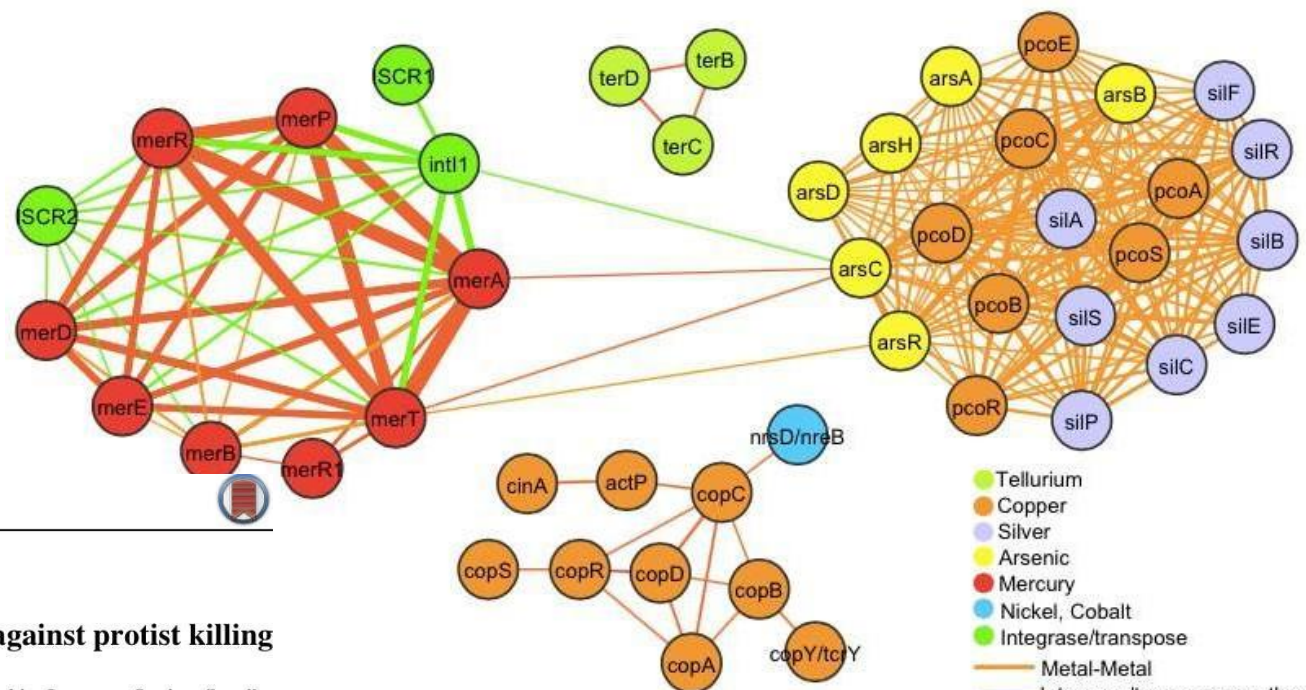
P.aeruginosa 2065: Δ*pcoA*::Cm

P.aeruginosa 3920: Δ*cueA*



Ars resistance often co-occurs on plasmids with copper resistance

As is used as toxin to kill bacteria

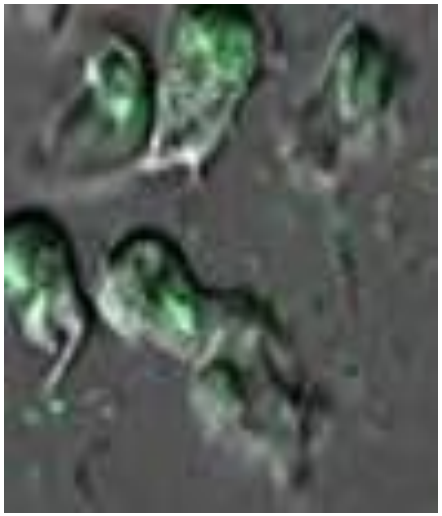


Biometals (2017) 30:307–311
DOI 10.1007/s10534-017-0003-4

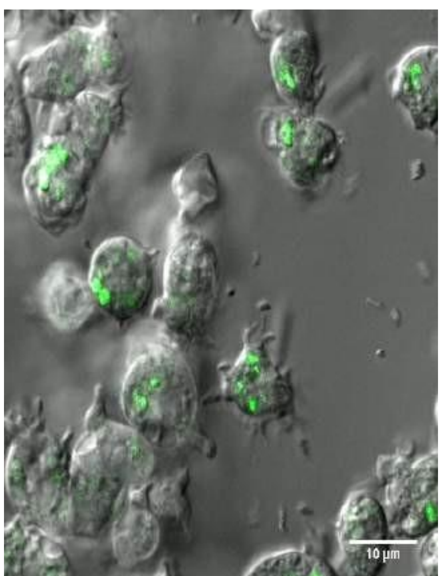
Bacterial resistance to arsenic protects against protist killing

Xiuli Hao · Xuanji Li · Chandan Pal · Jon Hobman · D. G. Joakim Larsson · Quaiser Saquib · Hend A. Alwathnani · Barry P. Rosen · Yong-Guan Zhu · Christopher Rensing

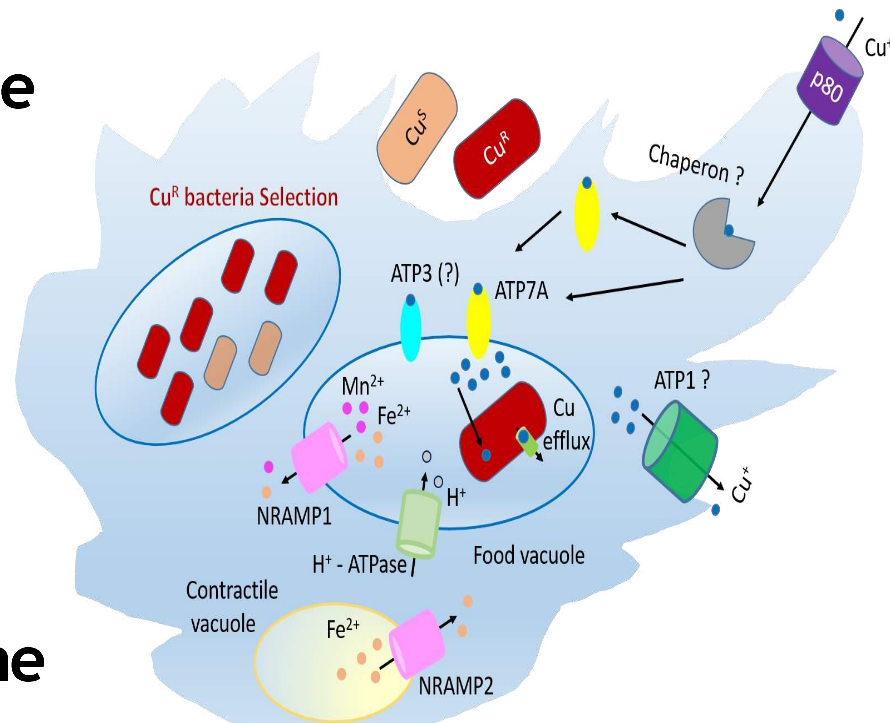
Zn and Cu dependent expression of gfp



Zn in phagosome



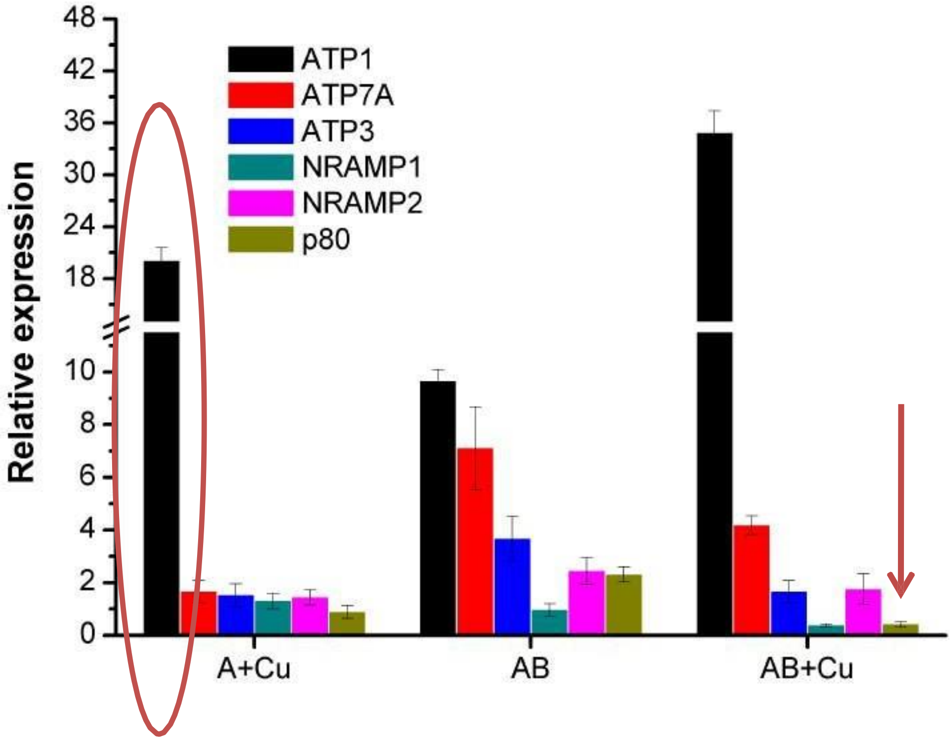
Cu in phagosome

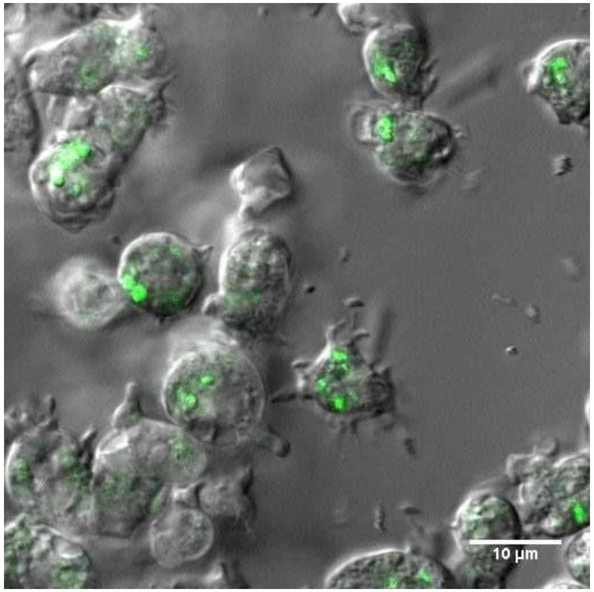


Molecular Microbiology (2016) 102(4), 628–641
doi:10.1111/mmi.13483
First published online 31 August 2016

A role for copper in protozoan grazing – two billion years selecting for bacterial copper resistance

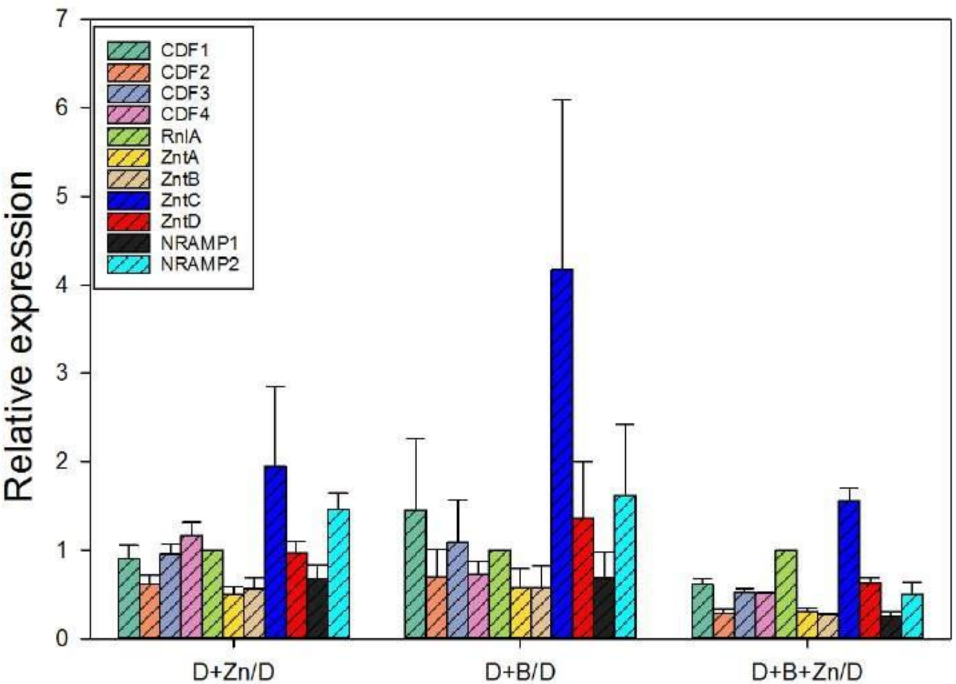
Cu(I) trafficking was triggered in *Dictyostelium* by bacteria ingestion

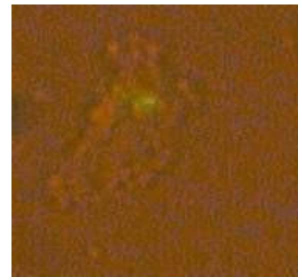


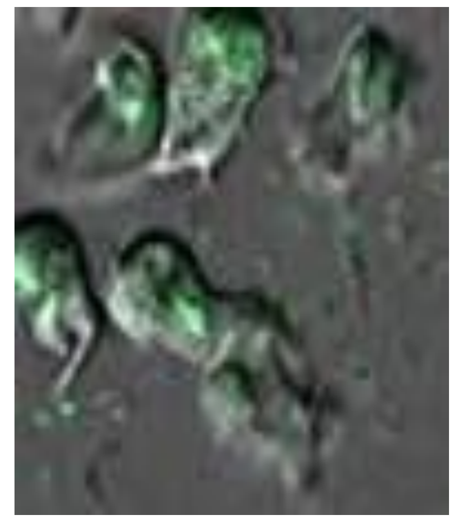


Dictyostelium + *P. putida* (pCuS-*GFP*)

Zn(II) trafficking was triggered in *Dictyostelium* by bacteria ingestion





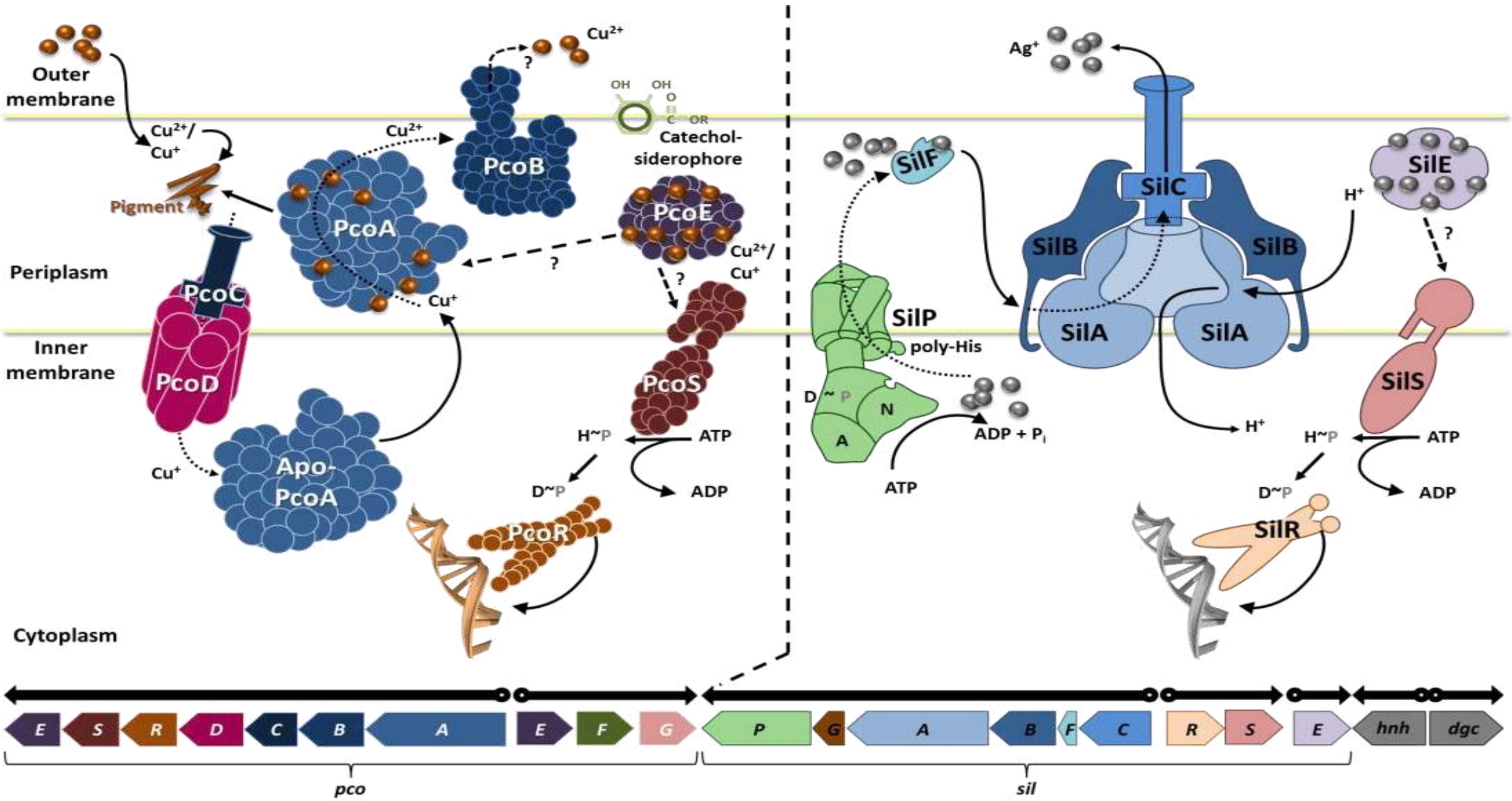


Dictyostelium + *M. metallidurans* (pCadA-*GFP*)

Cu and Zn fed to livestock

Daily feed (kg/day)	Copper (mg/kg diet)	Zinc (mg/kg diet)
Cattle (5.5–10)	10 (8)	30 (8)
Swine (1–2)	100–250 (11)	2000–3000 (11)
Poultry (0.1–0.2)	4–8 (12)	30–60 (12)

Cu-resistance & Cu-pathogenicity island?

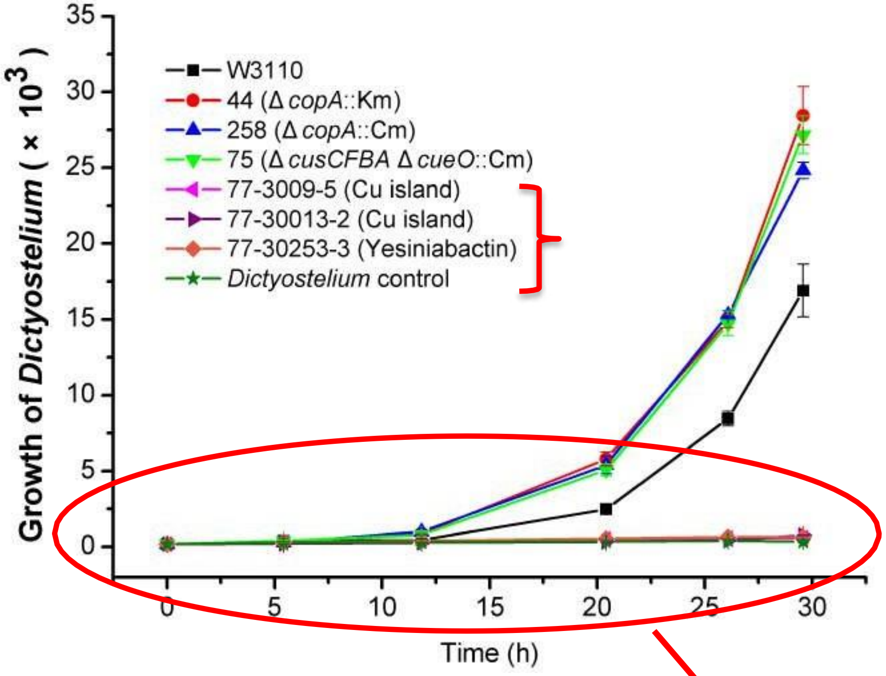


PcoESRDCBAE XX SilP CopG SilABFCRSEX

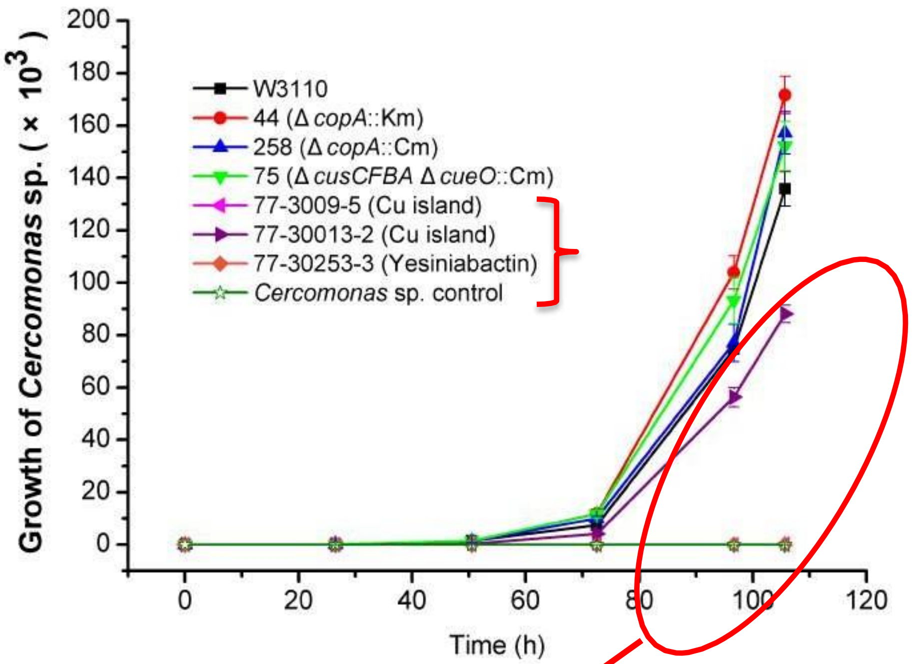
Hao et al., Appl Microbiol Biotechnol (2015)

Bacterial Cu^R determinants influence the growth of protozoa

Dictyostelium

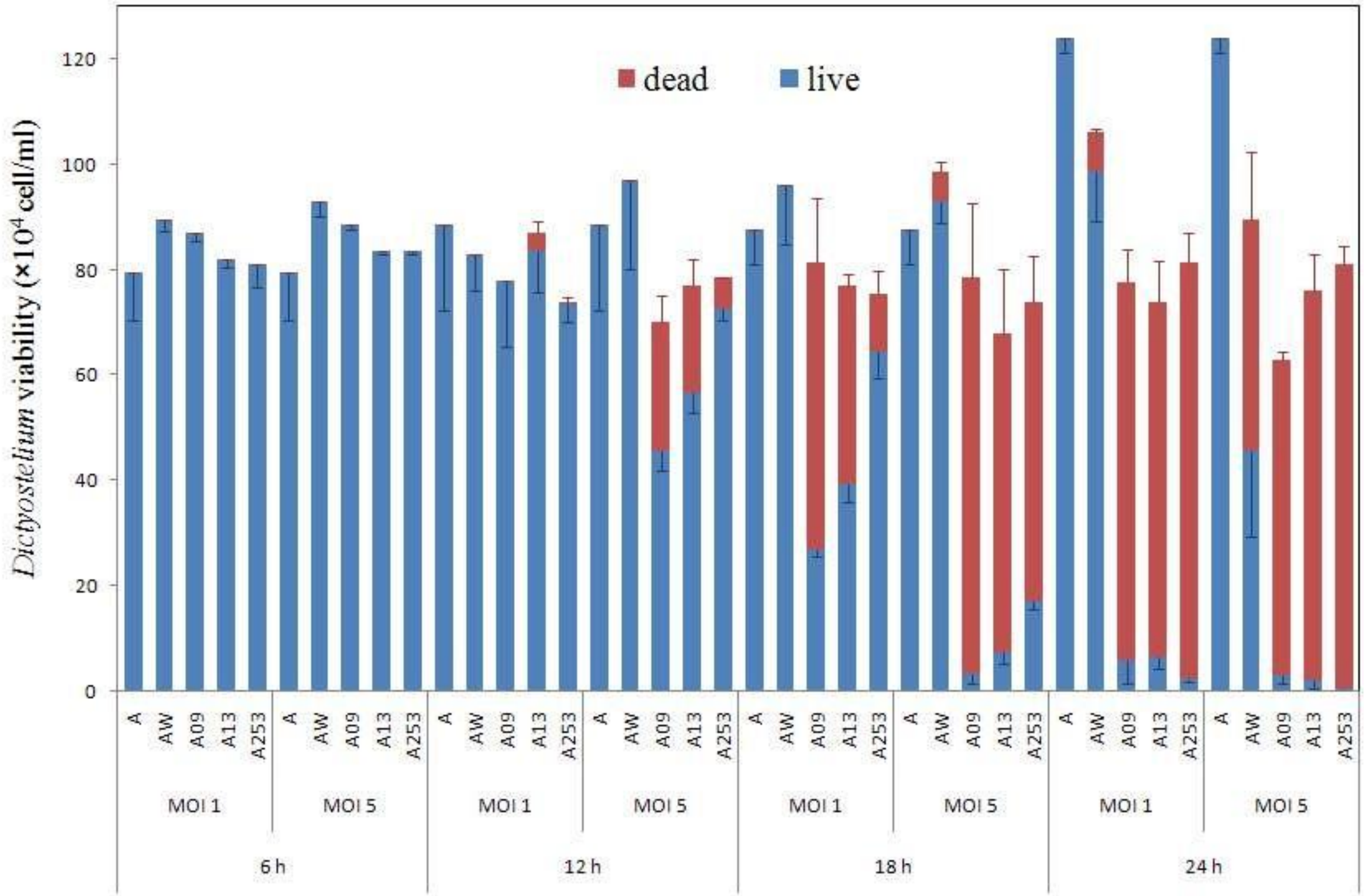


Flagellate

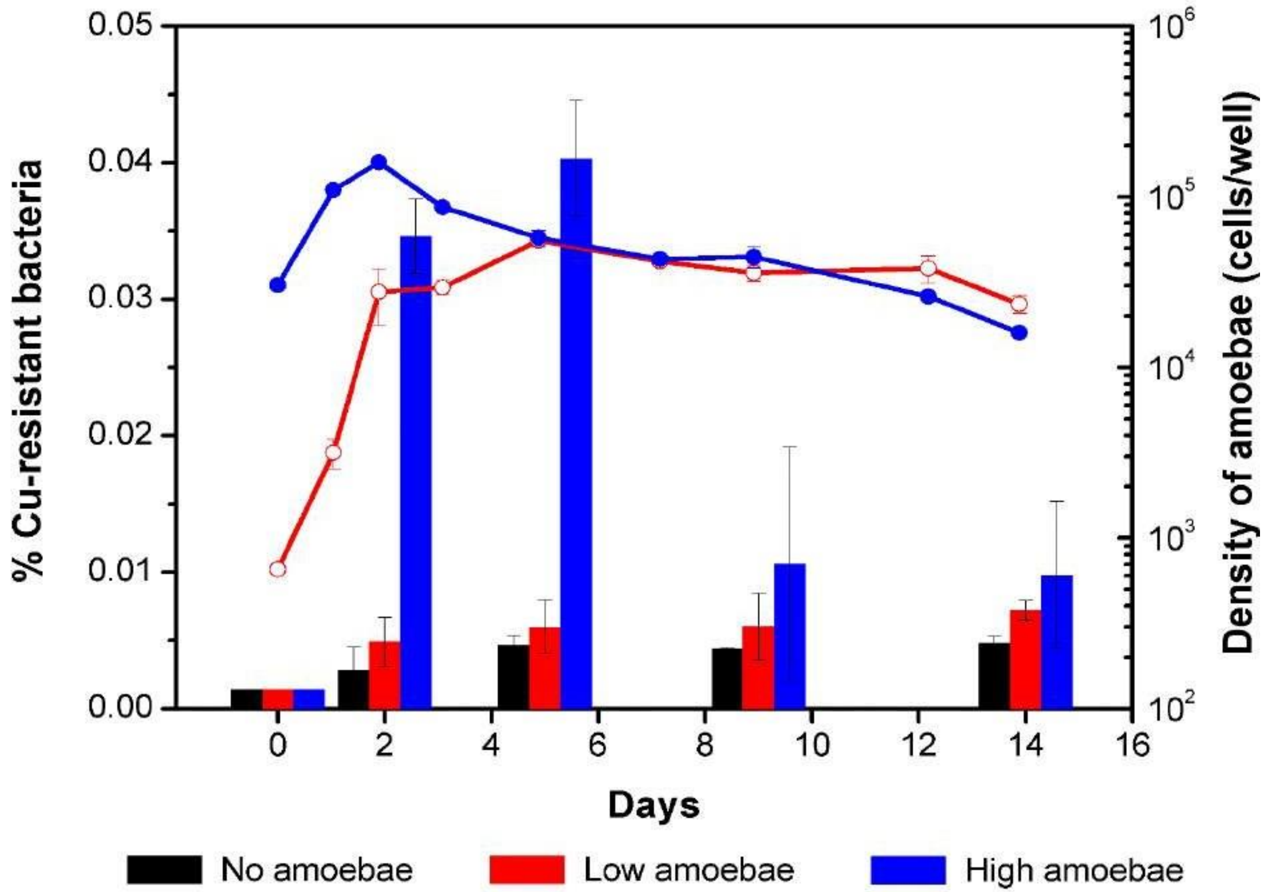


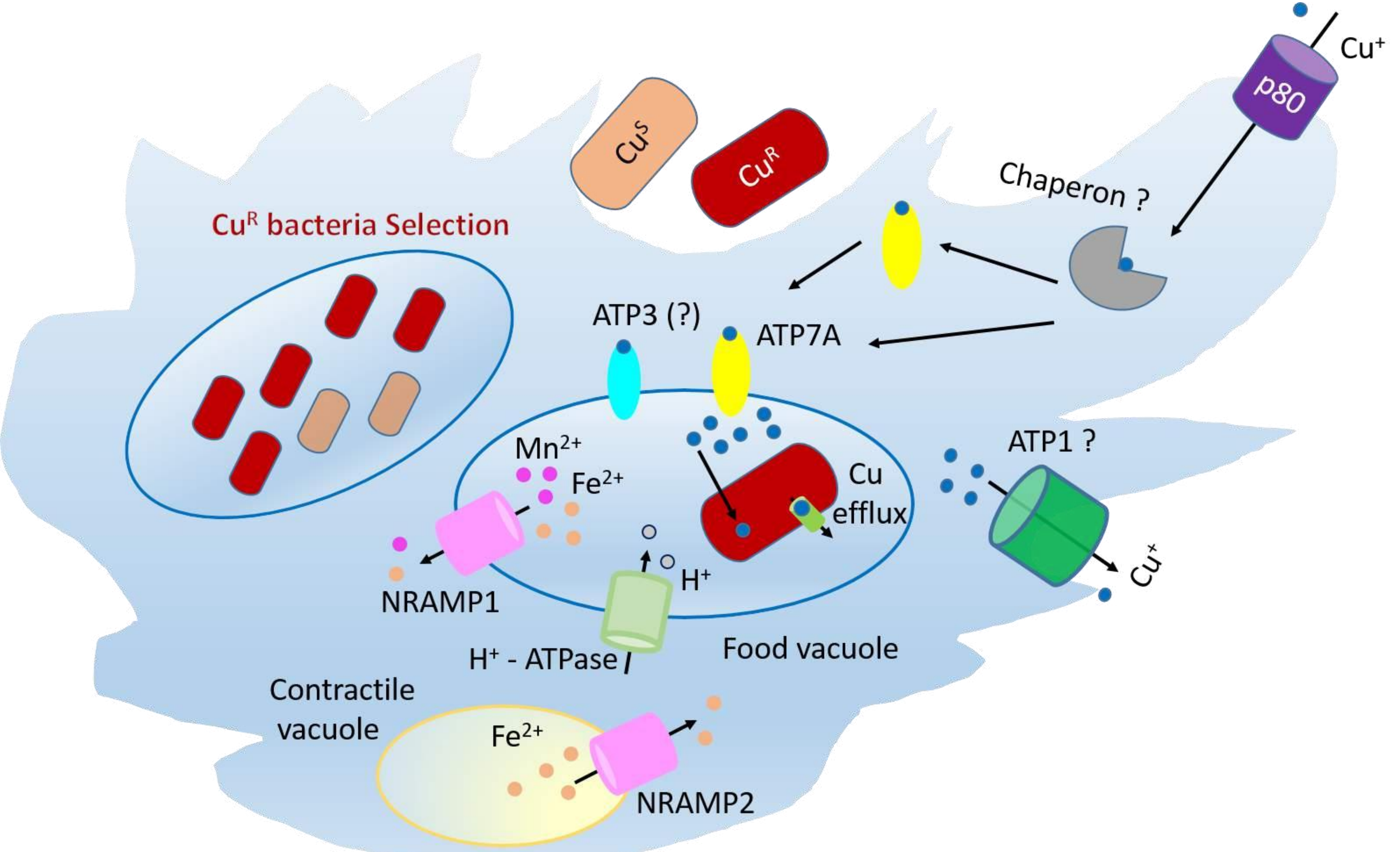
Little growth when fed with Cu^R strain containing Cu^R island

Dictyostelium viability with W3110 and three Cu^R *E. coli*



Selection of *Dictyostelium* grazing on Cu-resistant bacteria





Cu+
p80
Cu^S
Cu^R
Chaperon ?
Cu^R bacteria Selection
ATP3 (?)
ATP7A
ATP1 ?
Mn2+
Fe2+
Cu
efflux
Cu+
NRAMP1
H+
H+ - ATPase
Food vacuole
Contractile
vacuole
Fe2+
NRAMP2

Molecular Microbiology (2011)

doi:10.1111/j.1365-2958.2011.07758.x

The *cop* operon is required for copper homeostasis and contributes to virulence in *Streptococcus pneumoniae*

Sulman Shafeeq,[3†] Hasan Yesilkaya,[2†] Tomas G. Kloosterman,[3] Geetha Narayanan,[1] Michal Wandel,[3] Peter W. Andrew,[2] Oscar P. Kuipers[3] and Julie A. Morrissey[1*]

stasis also appears to be required for survival in the nasopharynx.

Introduction

Copper resistance is essential for virulence of *Mycobacterium tuberculosis*

Frank Wolschendorf[a], David Ackart[b], Tej B. Shrestha[c], Laurel Hascall-Dove[b], Scott Nolan[d], Gyanu Lamichhane[d], Ying Wang[a], Stefan H. Bossmann[c], Randall J. Basaraba[b], and Michael Niederweis[a,1]

[a]Department of Microbiology, University of Alabama at Birmingham, Birmingham, AL 35294; [b]Department of Microbiology, Immunology, and Pathology, Colorado State University, Fort Collins, CO 80523-1619; [c]Department of Chemistry, Kansas State University, Manhattan, KS 66506-0401; and [d]Tuberculosis Animal Research and Gene Evaluation Taskforce, The Johns Hopkins University School of Medicine, Baltimore, MD 21231

Edited by Emil C. Gotschlich, The Rockefeller University, New York, NY, and approved December 6, 2010 (received for review June 30, 2010)

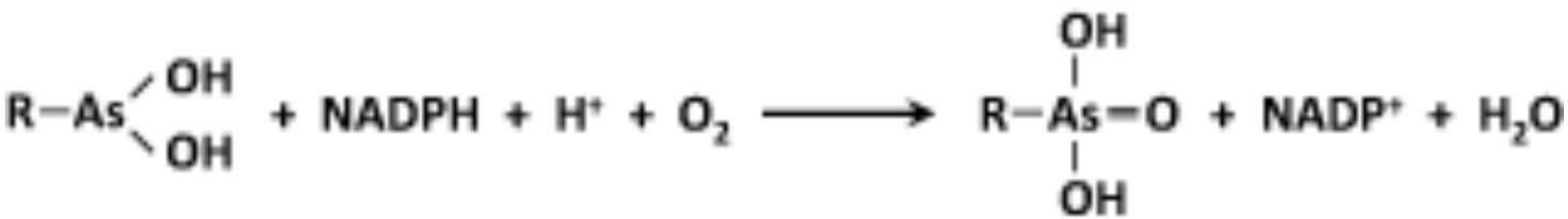
Role of Copper Efflux in Pneumococcal Pathogenesis and Resistance to Macrophage-Mediated Immune Clearance

Michael D. L. Johnson,[a] Thomas E. Kehl-Fie,[b] Roger Klein,[a*] Jacqueline Kelly,[a*] Corinna Burnham,[a] Beth Mann,[a] Jason W. Rosch[a]

Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, Tennessee, USA[a]; University of Illinois Urbana-Champaign, Department of Microbiology, Urbana, Illinois, USA[b]

Warum *merA*, *arsH*, *ter* operon?

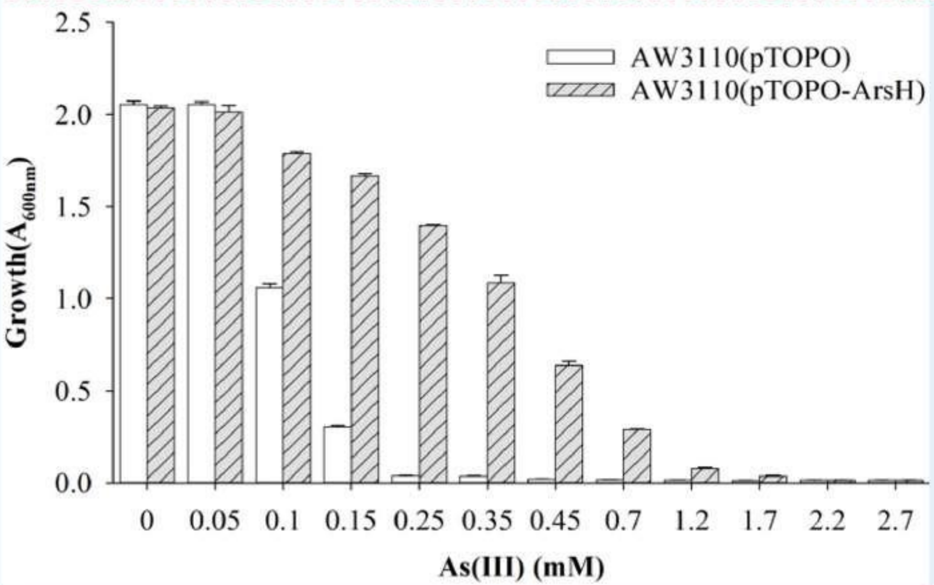
NADPH-dependent FMN reductase ArsH



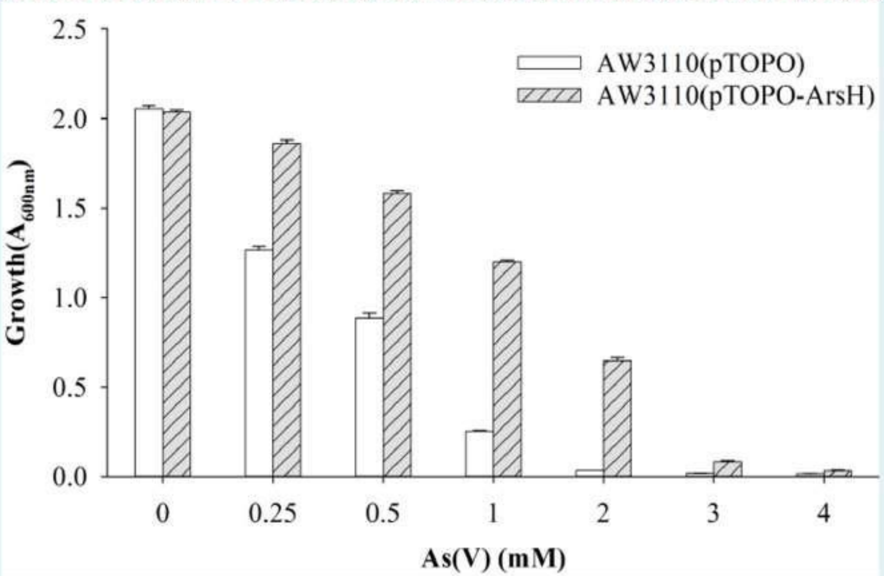
MMA(III) ist wesentlich toxischer als As(III)

Expession von ArsH macht Zellen resistenter gegen As(III), As(V), Sb(III) und Sb(V)

(A)



(B)

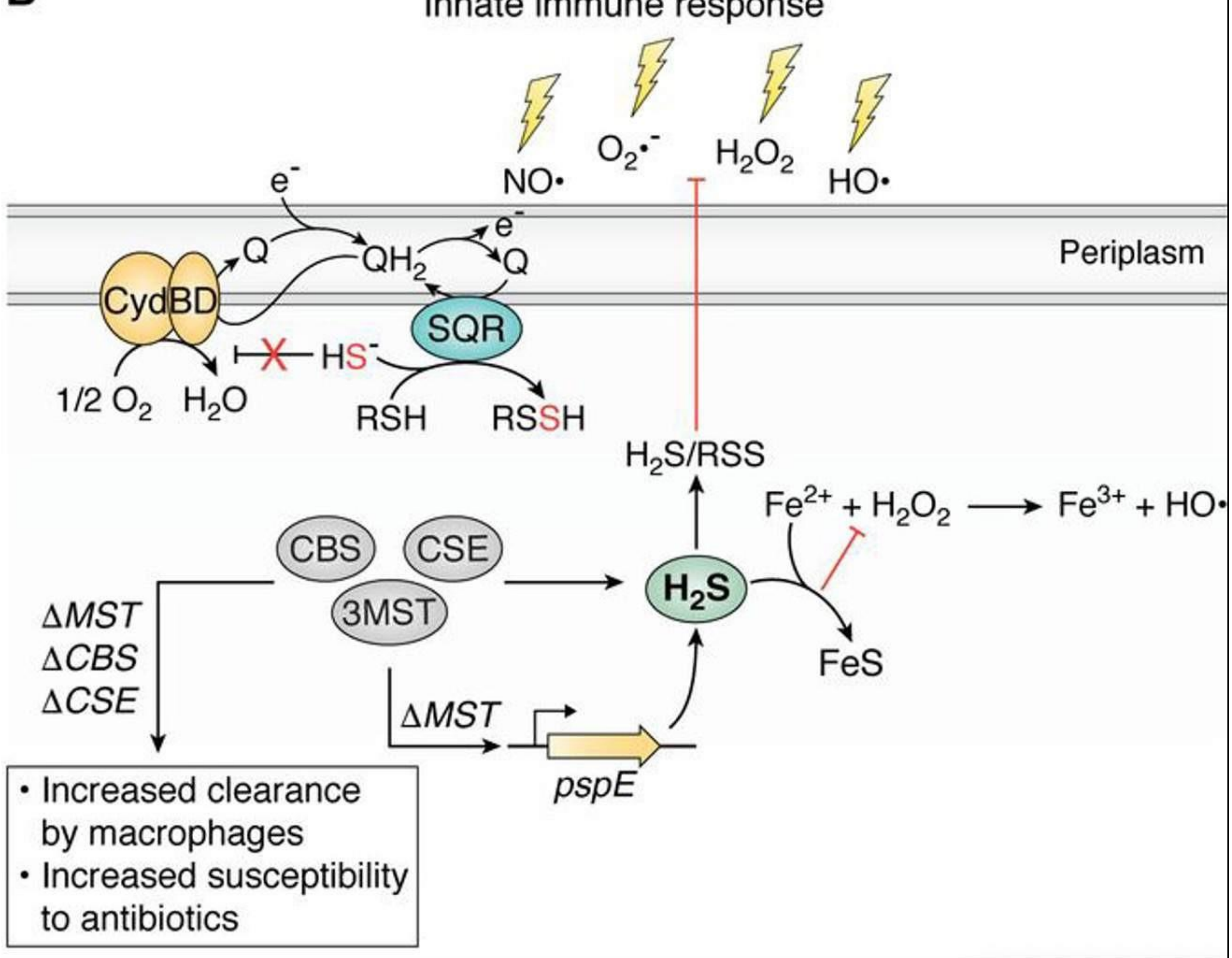


ArsH protects *Pseudomonas putida* from oxidative damage caused by exposure to arsenic

ArsH1 and ArsH2 protect P. putida *from oxidative stress caused by diamide*

Diamide thiol-specific oxidizing agent, which reacts with thiols and protein sulfhydryls, thereby oxidizing glutathione and promoting formation of disulfide bonds

B



Innate immune response
NO•
O2•-
H2O2
HO•
e-
Q
QH2
e-
Q
Periplasm
CydBD
SQR
HS-
1/2 O2
H2O
RSH
RSSH
H2S/RSS
Fe2+ + H2O2
Fe3+ + HO•
CBS
CSE
3MST
H2S
FeS
ΔMST
ΔCBS
ΔCSE
ΔMST
pspE
• Increased clearance by macrophages
• Increased susceptibility to antibiotics

Original article

Staphylococcus aureus responds to allicin by global *S*-thioallylation – Role of the Brx/BSH/YpdA pathway and the disulfide reductase MerA to overcome allicin stress

Vu Van Loi[a], Nguyen Thi Thu Huyen[a,1], Tobias Busche[a,b], Quach Ngoc Tung[a], Martin Clemens Horst Gruhlke[c], Jörn Kalinowski[b], Jörg Bernhardt[a,d], Alan John Slusarenko[c], Haike Antelmann[a,*]

Allicin provokes a strong thiol-specific oxidative and sulfur stress response in the *S. aureus* USA300 transcriptome

Biochemical assays indicate that MerA functions in allicin detoxification, the HypR-controlled disulfide reductase MerA

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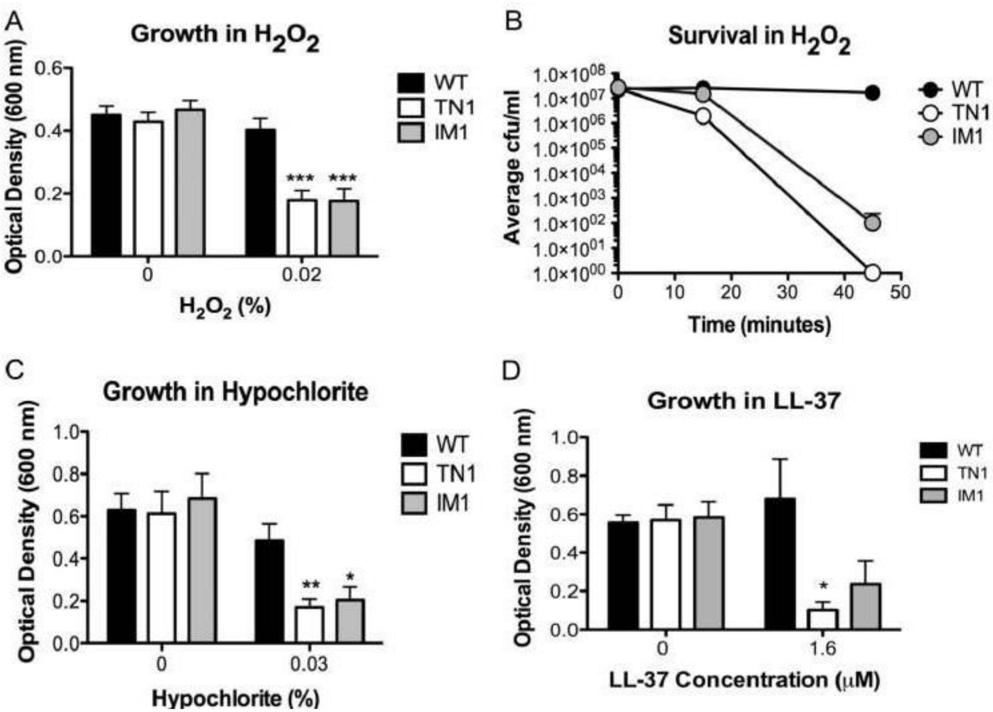
Novel Role for the *yceGH* Tellurite Resistance Genes in the Pathogenesis of *Bacillus anthracis*

Sarah E. Franks,[a] Celia Ebrahimi,[b] Andrew Hollands,[b] Cheryl Y. Okumura,[b] Raffi V. Aroian,[c] Victor Nizet,[b,d] Shauna M. McGillivray[a]

Department of Biology, Texas Christian University, Fort Worth, Texas, USA[a]; Department of Pediatrics,[b] Division of Biological Sciences,[c] and Skaggs School of Pharmacy and Pharmaceutical Sciences,[d] University of California San Diego, La Jolla, California, USA



Metall Resistenzen schuetzen vor Vergiftung durch Cu(I), Zn(II) und As(III), sind Virulenzfaktoren

Nebenjob der Metall Resistenzen ist der Schutz vor reaktiven Sauerstoffverbindungen

Selektionsvorteil auch ohne Vorhandensein vonMetallen, Selektionsvorteil