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IDENTIFICATION AND CHARACTERIZATION OF IRON ACQUISITION SYSTEMS IN Stenotrophomonas maltophilia

KALIDASAN VASODAVAN

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IDENTIFICATION AND CHARACTERIZATION OF IRON ACQUISITION SYSTEMS IN *Stenotrophomonas maltophilia*

By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

April 2017

"Gold is for the mistress, silver for the maid, copper for the craftsman, cunning at his trade, 'Good' said the Baron, sitting in his hall, 'but iron − cold iron − is master of them all.'
- Rudyard Kipling

This thesis is dedicated to my loving parents.
For their never-ending love, support and motivation

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

IDENTIFICATION AND CHARACTERIZATION OF IRON ACQUISITION SYSTEMS IN *Stenotrophomonas maltophilia*

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April 2017

Chair: Associate Professor Vasantha Kumari Neela, PhD
Faculty: Medicine and Health Sciences

Iron plays an essential role in bacterial pathogenesis most importantly shaping host-pathogen interactions. Host intracellular iron concentration not only serves as a signal for regulating the expression of iron acquisition systems in bacteria but also induce the secretion of a number of toxins and virulence factors in most pathogenic species. On the other hand, iron acquisition systems also act as candidates for prophylactics and therapeutics. A recently emerged environmental origin Gram-negative nosocomial pathogen *Stenotrophomonas maltophilia,* which is resistant to most antimicrobial agents pose major public health problems particularly among severely debilitated and immunocompromised individuals. Iron has shown to regulate biofilm formation, oxidative stress response and several pathogenic mechanisms in *S. maltophilia*. The present study is aimed at identifying various iron acquisition systems and iron source utilized during iron starvation in *S. maltophilia.*

The complete genome K279a, R551-3, D457 and JV3 were annotated through "Rapid Annotations using Subsystems Technology" (RAST) to identify putative iron acquisition systems. Polymerase chain reaction (PCR) assay was used to screen different targets involved in the iron acquisition systems. In order to investigate the effect of iron depletion and iron repletion on various genotypic and phenotypic properties of *S. maltophilia*, the isolates were subjected to iron starvation by growing in brain heart infusion (BHI) broth supplemented with the iron chelator, 100 µM 2,2'-dipyridyl (BHI-DIP) while for iron-repleted condition, BHI-DIP was supplemented with 100 µM $FeCl_3$. The iron acquisition genes expression under different iron conditions was investigated using NanoString Technologies. The production of siderophore in *S. maltophilia* was assessed by using "CAS agar diffusion (CASAD)" and $FeCl_3$ test. The spectrophotometric colorimetric assays such as Atkin's assay and Arnow's assay were performed in order to detect the chemical nature of siderophore. Utilization of hemin, hemoglobin, transferrin and lactoferrin during iron depletion in *S. maltophilia* was measured by growth kinetics.

The annotation of the complete genome K279a, R551-3, D457 and JV3 using RAST identified two putative subsystems involved in iron acquisition such as "Iron siderophore sensor & receptor system" and "Heme, hemin uptake and utilization systems/hemin transport system". Further molecular screening of each target revealed the clinical isolates contain complete putative targets in comparison with environmental isolates. The gene expression showed significant expression for FeSR, HmuT, Hup, ETFb, TonB and Fur under iron-depleted condition. *S. maltophilia* were found to produce catechol-type siderophores and utilized hemin, hemoglobin, transferrin and lactoferrin as iron sources.

In conclusion, the data in this research put together gives preliminary information on the iron acquisition systems and iron source utilized by *S. maltophilia* recommending further investigation in understanding their roles in pathogenesis, drug and vaccine development.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk ijazah Master Sains

PENGENALPASTIAN DAN PENCIRIAN SISTEM PEMEROLEHAN ZAT BESI DALAM *Stenotrophomonas maltophilia*

Oleh

KALIDASAN VASODAVAN

April 2017

Pengerusi: Profesor Madya Vasantha Kumari Neela, PhD
Fakulti: Perubatan dan Sains Kesihatan

Zat besi memainkan peranan penting dalam patogenesis bakteria terutamanya dalam membentuk interaksi perumah-patogen. Kepekatan zat besi intrasel perumah bukan sahaja berfungsi sebagai isyarat bagi pengawalaturan ekspresi sistem pemerolehan zat besi dalam bakteria, tetapi juga mendorong rembesan beberapa toksin dan faktor virulens dalam kebanyakan spesis patogenik. Di samping itu, sistem pemerolehan zat besi juga bertindak sebagai calon untuk profilaksis dan terapeutik. Kemunculan *Stenotrophomonas maltophilia* asalan alam sekitar Gram negatif patogen nosokomial, yang mempunyai kerintangan terhadap kebanyakan ejen antimikrob menimbulkan masalah kepada kesihatan awam khususnya dalam kalangan individu yang lemah dan terimunokompromi. Zat besi berfungsi dalam mengawalatur pembentukan biofilem, tindak balas tekanan oksidatif dan beberapa mekanisme patogenik dalam *S. maltophilia*. Kajian ini bertujuan untuk mengenal pasti pelbagai sistem pemerolehan dan sumber zat besi yang digunakan semasa kekurangan zat besi dalam *S. maltophilia*.

Genom lengkap K279a, R551-3, D457 dan JV3 telah dianotasi menggunakan “Rapid Annotation using Subsystems Technology (RAST)” untuk meramal sistem pemerolehan zat besi. Asai reaksi rantai polimerase (PCR) telah digunakan untuk menyaring sistem pemerolehan zat besi. Untuk menyiasat kesan kekurangan dan berlebihan zat besi pada pelbagai sifat genotip dan fenotip *S. maltophilia*, isolat tertakluk kepada kekurangan zat besi dengan membiak dalam kaldu penginfusan otak-jantung (BHI) ditambah dengan pengkelat zat besi, sebanyak 100 μM 2,2'-dipyridyl (BHI-DIP), manakala bagi keadaan zat besi berlebihan, BHI-DIP telah ditambah dengan 100 μM $FeCl_3$. Ekspresi gen pemerolehan zat besi dalam keadaan zat besi yang berbeza dikaji melalui “NanoString Technologies”. Penghasilan siderofor dalam *S. maltophilia* dinilai dengan menggunakan "peresapan CAS agar (CASAD)" dan ujian $FeCl_3$. Asai kolorimetri spektrofotometri seperti Atkin dan Arnow telah dijalankan untuk mengesan sifat kimia siderofor. Penggunaan hemin, hemoglobin, transferin dan laktoferin semasa susutan zat besi diukur melalui kinetik pertumbuhan

Anotasi genom lengkap K279a, R551-3, D457 dan JV3 menggunakan RAST mengenal pasti dua subsistem yang berkemungkinan terlibat dalam sistem pemerolehan zat besi seperti "Iron siderophore sensor & receptor system" dan "Heme, hemin uptake and utilization systems/hemin transport system". Saringan molekul bagi setiap sasaran menunjukkan, pencilan klinikal mengandungi kesemua sasaran ramalan berbanding dengan pencilan alam sekitar. Ekspresi gen menunjukkan ekspresi signifikan bagi FeSR, HmuT, Hup, ETFb, TonB dan Fur dalam keadaan kekurangan zat besi. *S. maltophilia* didapati menghasilkan siderofor jenis katekol dan menggunakan hemin, hemoglobin, transferin dan laktoferin sebagai sumber zat besi.

Kesimpulannya, kesemua data dalam kajian ini memberikan maklumat awal mengenai sistem pemerolehan dan sumber zat besi yang digunakan oleh *S. maltophilia* yang mencadangkan siasatan lanjutan dalam memahami peranan mereka dalam patogenesis, perkembangan ubatan dan vaksin.

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I certify that a Thesis Examination Committee has met on 3 April 2017 to conduct the final examination of Kalidasan a/l Vasodavan on his thesis entitled "Identification and Characterization of Iron Acquisition Systems in *Stenotrophomonas maltophilia*" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

Members of the Thesis Examination Committee were as follows:

Chee Hui Yee, PhD
Senior Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Leslie Than Thian Lung, PhD
Senior Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Internal Examiner)

Sheila Nathan, PhD
Professor
Universiti Kebangsaan Malaysia
Malaysia
(External Examiner)

RUSLI HAJI ABDULLAH, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 30 July 2018

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

Vasantha Kumari Neela, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Suresh Kumar Subbiah, PhD
Senior Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Rukman Awang Hamat, MBBS, MPath
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

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ROBIAH BINTI YUNUS, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

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Signature: _____
Name of Member of
Supervisory Committee: Suresh Kumar Subbiah

Signature: _____
Name of Member of
Supervisory Committee: Rukman Awang Hamat

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PIPES	1,4-piperazinediethanesulfonic acid
Abbrev.	Abbreviation
ATP	Adenosine triphosphate
α	Alpha
ATCC	American Type Culture Collection
T_a	Annealing temperature
~	Approximate
ABC	ATP-binding cassette
Bfr	Bacterioferritin
bp	Base pair
BLAST	Basic Local Alignment Search Tool
BCCM	Belgian Coordinated Collections of Microorganisms
β	Beta
β-ME	Beta-mercaptoethanol
BRC	Bioinformatics Resource Centre
BHI	Brain heart infusion
CO	Carbon monoxide
CDF	Cartridge Definition File
CASAD	CAS agar diffusion
CVC-BSI	Catheter-related blood stream infection
CSF	Cerebrospinal fluid
CAS	Chrome azurol sulphonate
CFU	Colony forming unit
CTRL (-)	Control (negative) for CASAD
CTRL (+)	Control (positive) for CASAD
CF	Cystic fibrosis
C	Cytoplasm
CM	Cytoplasmic membrane
°C	Degree celsius
df	Degree of freedom
DNase	Deoxyribonuclease
DNA	Deoxyribonucleic acid
DSF	Diffusible signal factor
DHB	Dihydroxybenzoic acid
DtxR	Diptheria toxin repressor
Dp	DNA-binding protein
ETFb	Electron transfer flavoprotein, beta subunit
ETC	Electron transport chain
EDDHA	Ethylenediamine-di (o - hydroxyphenylacetic acid)
ECF	Extracytoplasmic function
fM	Fentomolar
$FeCl_3$	Ferric chloride
Fe^{3+}	Ferric iron
ExbB	Ferric siderophore transport system, biopolymer transport protein
TonB	Ferric siderophore transport system, periplasmic binding protein
Fur	Ferric uptake regulation protein FUR

Fe/Fe^{3+}-S	Ferric-siderophore
Fn	Ferritin
Fe^{2+}	Ferrous iron
Fe	Ferum (iron)
FOV	Field of View
FAD	Flavin adenine dinucleotide
FMN	Flavin mononucleotide
F	Forward
f	Frequency
g	Gram
Hpt	Haptoglobin
Hm	Heme
HmuV	Heme ABC transporter, ATPase component
HmuT	Heme ABC transporter, cell surface heme and hemoprotein receptor
HmuU	Heme ABC transporter, permease protein
HemO/HO	Heme oxygenase, associated with heme uptake
hmu	Heme uptake locus
Hm-Hpx	Heme-hemopexin
Htp	Hemin transport protein
Hup	Hemin uptake protein
Hb	Hemoglobin
Hb-Hpt	Hemoglobin-haptoglobin
Hpx	Hemopexin
H	Hemophore
Hp	Hepcidin
HDTMA	Hexadecyltrimethylammonium bromide
h	Hour
HIV	Human immunodeficiency virus
HCl	Hydrochloric acid
H_2O_2	Hydrogen peroxide
Hyp1	Hypothetical protein related to heme utilization
I.D.	Identification
IMP	Integral membrane protein
IDT	Integrated DNA Technologies
ICU	Intensive care unit
IL	Interleukin
IM	Intramuscular
IV	Intravenous
ID	Iron deficiency
IROMP	Iron regulated outer membrane protein
IRP	Iron regulatory protein
Irr	Iron response regulator
FeSR	Iron siderophore receptor protein
FeSS	Iron siderophore sensor protein
IDG	Iron-depleted growth
IDB	Iron-depleted uninoculated broth
IRG	Iron-repleted growth
IRB	Iron-repleted uninoculated broth
IRE	Iron-responsive element

kDa	Kilodalton
kg	Kilogram
LMG	Laboratory for Microbiology
Lf	Lactoferrin
Lbp	Lactoferrin-binding protein
Lcn-2	Lipocalin-2
LPS	Lipopolysaccharide
LPSN	List of Prokaryotic Names with Standing in Nomenclature
LEAP1	Liver-expressed antimicrobial peptide
LB	Luria-Bertani
Mur	Manganese uptake regulator
T_m	Melting temperature
MET	Metallic cations
MR-VP	Methyl-red-Voges Proskauer
µg	Microgram
µl	Microliter
µM	Micromolar
mg	Milligram
ml	Milliliter
MOH	Ministry of Health
MEGA	Molecular Evolutionary Genetics Analysis
MDRO	Multiple-drug-resistant organism
CYPOR	NADPH-cytochrome P450 oxidoreductase
nm	Nanometer
nM	Nanomolar
NCBI	National Centre for Biotechnology Information
NMPDR	National Microbial Pathogen Data Resource
Nramp1	Natural resistance-associated macrophage protein-1
NEAT	Near transporter
NC	Negative control
NET	Neutrophil extracellular trap
NGAL	Neutrophil gelatinase-associated lipocalin
Nur	Nickel uptake regulator
NRPS	Nonribosomal peptide synthatases
NTC	Non-template control
NBD	Nucleotide-binding domains
OD	Optical density
OM	Outer membrane
OMP	Outer membrane protein
OMRP	Outer membrane receptor protein
Rp2	Outer membrane receptor proteins, mostly Fe transport
PAI	Pathogenicity island
PATRIC	Pathosystems Resource Integration Centre
%	Percentage
PBP	Periplasmic binding protein
PS	Periplasmic space
PerR	Peroxide response regulator
PBS	Phosphate buffer saline
PCR	Polymerase chain reaction
PMN	Polymorphonuclear neutrophil

Pos	Position
PC	Positive control
pH	Potential of hydrogen
DyP	Predicted dye-decolorizing peroxidase, encapsulated subgroup
PPI	Protein-protein interaction
PMF	Proton-motive force
QC	Quality control
RAST	Rapid Annotations using Subsystem Technology
ROS	Reactive oxygen species
RME	Receptor mediated endocytosis
RBC	Red blood cell
RefSeq	Reference Sequence
x g	Relative centrifugal force (gravity)
RCC	Reporter Code Counts
RFL	Reporter Library File
R	Reverse
RT	Reverse transcription/transcriptase
r.p.m	Revolutions per minute
RNase	Ribonuclease
RNA	Ribonucleic acid
rRNA	Ribosomal ribonucleic acid
n	Sample size
Scn	Siderocalin
S	Siderophore
σ	Sigma
FeSreg	Sigma factor ECF subfamily
SCV	Small colony variant
SDS-PAGE	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
NaOH	Sodium hydroxide
SCL	Solute carrier
spp.	Species (plural)
sp.	Species (singular)
SS-PCR	Species-specific polymerase chain reaction
SS	Stainer-Scholte
SD	Standard deviation
S. maltophilia	*Stenotrophomonas maltophilia* (SM)
FCR	TonB-dependent hemin, ferrichrome receptor
TBDT	TonB-dependent transporters
tRNA	Transfer ribonucleic acid
Tf	Transferrin
TfR	Transferrin receptor
TSAT	Transferrin saturation
Tbp	Transferrin-binding protein
TMD	Transmembrane domains
TCA	Tricarboxyclic acid cycle
TBE	Tris-borate-EDTA
TE	Tris-EDTA
TB	Tuberculosis
TNF-α	Tumor necrosis factor-α

UV	Ultraviolet
UV-Vis	Ultraviolet–visible
USB	Universal serial bus
UKMMC	Universiti Kebangsaan Malaysia Medical Centre
UMMC	University Malaya Medical Centre
VIA	Vancomycin, imipenem and amphotericin B
VAP	Ventilator-associated pneumonia
VOC	Volatile organic compound
V	Volt
v/v	Volume per volume
w/v	Weight per volume
WHO	World Health Organization
XMSM	*Xanthomonas maltophilia* Selective Medium
Zur	Zinc uptake regulator

CHAPTER 1

INTRODUCTION

Iron (Fe) is a precious element for most microorganisms and also required for host metabolism and other important functions (Cairo et al. 2006). For bacteria, approximately 10^{-16} to 10^{-17} molar of iron are required per cell to support their biological functions (Braun 2001; Schaible and Kaufmann 2004). Iron is essential in the preservation of cellular morphology, DNA and RNA biosynthesis, cellular growth and proliferation, catalysis of tricarboxylic acid cycle (TCA), electron transport chain (ETC), oxidative phosphorylation, nitrogen fixation and many more. Various metabolic products such as porphyrins, toxins, vitamins, cytochromes, siderophores, aromatic compounds, etc. are produced when iron concentration varies. Peroxidase, catalases and superoxide dismutase that are capable of scavenging the harmful radicals also contain iron in order to maintain the cellular physiology (Messenger and Barclay 1983).

In general, the mammalian hosts acquire iron exclusively from dietary intake, whereby approximately 1 to 2 mg of iron will be absorbed from the duodenum and bound to transferrin (Tf), the primary plasma iron carrier protein (Andrews and Schmidt 2007; Dunn et al. 2007). On an average, the human adult contains approximately 3 to 4 g of iron and the largest pool is held within circulating erythrocytes (1800 mg), followed by tissues predominately the liver (1000 mg), reticuloendothelial cells (200 to 1000 mg), bone marrow (300 mg) and myoglobin (300 mg) (Hentze et al. 2004; Drygalski and Adamson 2013). However, in a higher cellular concentration, iron is potentially toxic when it reacts with oxygen, releasing the reactive oxygen species (ROS) via the Fenton and Haber-Weiss reaction. These free radicals are further capable of damaging membrane lipids, proteins and DNA of the cell (Wooldridge and Williams 1993; Krewulak and Vogel 2008).

To successfully sustain an infection in the human host, the bacteria require a continuous supply of iron. As the vertebrate host sequesters the free iron to prevent cellular damage by ROS, iron is largely bound to high-affinity proteins (Marx 2002; Braun and Hantke 2011). Consequently, the availability of free iron is greatly reduced and the bacterial pathogens encounter a period of iron starvation upon invading their hosts. Thus, to avoid invasion of pathogenic microorganisms, the host restrict access to the iron in a process called “nutritional immunity”. Therefore, it is important for pathogens to sense the restriction and in return maintain a controlled balance of uptake and acquisition to ensure initiation of bacterial pathogenesis (Skaar 2010).

The emergence of *Stenotrophomonas maltophilia* as a paradigm of multiple-drug-resistant organisms (MDROs), an opportunistic pathogen with an environmental origin has all underscored the need for an investigation. The pathogen exhibits intrinsic and acquired resistance to a broad spectrum of antimicrobial agents and reveals high virulence in order to establish infections. Thus, this situation puts a greater risk among

patients with prolonged hospitalization, intensive care unit (ICU) admission, malignancy, immunosuppressed and exposed mucus membrane. Another greater challenge faced by the physician, infectious disease specialist, infection control unit as well as a microbiologist is the development of new strategies for the prevention of infections. *S. maltophilia* is known to be affecting various systems in the human host and competing with the host for nutrients, especially iron for its replication and multiplication which needs an immediate investigation (Senol 2004; Looney et al. 2009).

Despite its clinical relevance, very little is known (Huang and Lee Wong 2007) and only a few preliminary iron studies have been reported in *S. maltophilia* (Chhibber et al. 2008; Mokracka et al. 2011; García et al. 2012). Iron levels in *S. maltophilia* play an important role in biofilm formation, oxidative stress response, outer membrane proteins (OMPs) expression, diffusible signal factor (DSF) and other virulence profile (García et al. 2015). Genetic factors that possibly contribute to putative iron acquisition and mechanism of uptake by *S. maltophilia* is still unknown (Adamek et al. 2014).

In an earlier study, the virulence of uropathogenic mutant *Escherichia coli* strain CFT073 was affected, when the species was unable to synthesize the outer membrane receptor proteins (OMRPs) when tested in the mouse kidney model, like the ability to uptake iron was inhibited (Torres et al. 2001). Similarly, inhibition of biosynthesis of the iron chelator, siderophore, was achieved through the action of a small molecule, 5'-*O*-(*N*-salicylsulfamoyl) adenosine (salicyl-AMS) among *Mycobacterium tuberculosis* and *Yersinia pestis* (Ferreras et al. 2005). Likewise, *S. maltophilia* still finds ways to acquire iron, it is crucial to inhibit the pathogen's ability to uptake iron by understanding the potential mechanism(s) used to obtain these precious metal so that similar approaches could be applied in targeting the iron uptake.

Moreover, it was reported that some OMRPs for siderophore transport could bind and transport antibiotics. As *S. maltophilia* has an increased resistance to many antimicrobial agents, this "dual functions" could provide benefits in catering concerns toward resistance issues. Through the "Trojan Horse" strategy (Möllmann et al. 2009), the iron transport abilities of siderophores has also shown to carry drugs into cells by preparing conjugates called sideromycins between siderophores and antimicrobial agents (Braun et al. 2001; Braun and Braun 2002; Nagoba and Vedpathak 2011; Ali and Vidhale 2013). Deferoxamine (brand name: Desferal®), a siderophore produced by *Streptomyces pilosus* have been found to be useful in the treatment of acute iron intoxication and chronic iron overload diseases such as hemochromatosis, sickle cell disease and thalassemia major (Piga et al. 2006; Brittenham 2011). Studying iron transport can also have agricultural implications. In agriculture, siderophore can be used as a biocontrol, biosensor, bioremediation, chelation agents, weathering soil minerals and enhancing plant growth (Ahmed and Holmström 2014).

Therefore, the current study is aimed to identify and characterize iron acquisition systems in *S. maltophilia* that could provide fundamental information for drug target, drug delivery, therapeutic, diagnostic and agriculture approaches.

1.1 Hypothesis

S. maltophilia utilizes iron as their source of nutrient and uptake through siderophore- and heme-mediated iron acquisition systems. The findings will be a baseline for understanding *S. maltophilia* pathogenesis, iron acquisition systems and type of iron sources utilized to be used as a drug target, for drug delivery, treatment and as a vaccine candidate.

1.2 Objectives

1.2.1 General objective

To identify and investigate putative iron acquisition systems and iron source utilized by *S. maltophilia* isolates.

1.2.2 Specific objectives

1. To identify and screen putative targets related to iron acquisition systems in *S. maltophilia*.
2. To investigate the iron acquisition genes expression in *S. maltophilia* under iron-depleted and iron-repleted conditions.
3. To detect the production of siderophores in *S. maltophilia* grown under iron-depleted and iron-repleted conditions and their chemical nature.
4. To determine the iron source(s) used by *S. maltophilia* during iron depletion.

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