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Review Cation Diffusion Facilitator family: Structure and function



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ABSTRACT

The Cation Diffusion Facilitators (CDFs) form a family of membrane-bound proteins capable of transporting zinc and other heavy metal ions. Involved in metal tolerance/resistance by efflux of ions, CDF proteins share a two-modular architecture consisting of a transmembrane domain (TMD) and C-terminal domain (CTD) that protrudes into the cytoplasm. Discovery of a Zn²⁺ and Cd²⁺ CDF transporter from a marine bacterium *Maricaulis maris* that does not possess the CTD questions current perceptions regarding this family of proteins. This article describes a new, CTD-lacking subfamily of CDFs and our current knowledge about this family of proteins in the view of these findings.

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1. Divalent metal cations and the importance of their transport

Many heavy metal ions constitute essential trace elements (known as micronutrients) in many biological systems. Such elements perform vital biological functions at low levels but can cause toxic effects at higher cellular concentrations. Consequently, living organisms have evolved transport mechanisms for the active uptake and/or extrusion of these ions in order to control their intracellular levels [94]. Essential trace elements commonly found in cells include zinc, cobalt, iron, manganese and copper and although other heavy metal ions are found in cells they have yet to have clear physiological functions defined. Focusing on the known essential trace elements, cobalt is required in vitamin B12 and other cobalamins [112] while manganese is essential in many

enzymes and is necessary for glucose metabolism [91]. Essential in the electron transport chain, iron and copper are found at the center of cytochromes and in the active site of cytochrome *c* oxidases, respectively [48,109]. Many enzymes contain zinc in the active center or in other structurally important sites. In addition to enzyme catalysis, zinc has also been shown to be crucial for cell growth, development and differentiation by contributing to processes such as gene expression, DNA synthesis, hormone storage and release, neurotransmission, memory and apoptosis [4]. In humans, zinc has been found to be required for the function of various bone growth hormones such as testosterone and thyroid hormones, and indeed other vital hormones, including insulin [8].

Four major families of zinc transporting proteins have been identified: (i) RND (Resistance, Nodulation and Division) multidrug efflux transporters, (ii) P-type ATPases (iii) ZIP (ZRT, IRT-like Protein) transporters and (iv) CDF (Cation Diffusion Facilitator) transporters. While the RND type transporters are only found in a few Gram-negative bacteria [37], the zinc transporting ATPases are found widely in bacteria and plants [108,104]. On the other hand ZIPs are mammalian transporters [47] and the CDFs build an ubiquitous family of proteins found in all major phyla of living organisms [74]. The latter have evolved a strong preference for the trafficking of zinc ions in many biological systems. In humans, zinc homeostasis is mediated mainly by two zinc transporter families, the zinc import proteins (ZIP/Slc39) and CDF proteins for zinc export (ZnT/Slc30). To date, 14 ZIP and 10 ZnT proteins have been identified [24]. The disturbed zinc homeostasis often caused by a mutation in one or more zinc transporters has been associated

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Abbreviations: CDF, Cation Diffusion Facilitator; TMD, transmembrane domain; CTD, C-terminal domain; ITC, isothermal titration calorimetry; SEC-MALS, size exclusion chromatography multi-angle light scattering; IL2, intracellular loop 2; ZnT, zinc transporter; RND, resistance nodulation and division; SIC, solute carrier; Zrc, zinc resistance conferring; EL, extracellular loop; SAXS, small angle X-ray scattering; MD, Molecular Dynamics

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with a number of diseases such as neonatal zinc deficiency, Alzheimers Disease, diabetes and prostate cancer. The pathophysiological roles of ZnT (Zinc Transporter) proteins have been extensively reviewed recently in [42].

This review will summarize the current knowledge of the CDF transporters in the view of the recently described subfamily of CDFs that lack the C-terminal cytoplasmic domain (CTD).

2. CDFs - more than heavy metal efflux proteins

The CDF family of transporters was first described in the late 1990s and its first characterized member, CzcD, shown to play a role in heavy metal resistance in Cupriavidus metallidurans [73,80] (formerly Alcaligenes eutrophus, Ralstonia metallidurans, Wautersia metallidurans strain CH34 [31]). Members of this ubiquitous family of proteins can be found in bacteria, archaea, and eukaryotes [74]. Although initially believed to just transport Zn²⁺, Cd^{2+} and Co^{2+} , CDFs have been shown to mediate the transport of other divalent metal ions including Mn²⁺, Ni²⁺ and Fe²⁺ [72,87,18,83], though the human members of this family, the ZnT proteins, mainly transport Zn²⁺. Plant CDFs are commonly called MTPs (Metal Tolerance Proteins) and have primarily been characterized as Mn²⁺ transport proteins. There are a number of exceptions in terms of metal specificity within the CDF family. CzcD from Bacillus subtilis is reported to play a role in Cu²⁺ tolerance and PbtF from Achromobacter xylosoxidans A8 reported to play a role in Pb²⁺ efflux, however more characterization is needed in both cases [71,39].

Based on early phylogenetic analysis, the CDF family was divided into three major groups according to metal ion specificity: (1) Mn²⁺-transporting CDFs, (2) Fe²⁺/Zn²⁺-transporting CDFs and (3) CDFs transporting Zn^{2+} and other metal ions but not Fe^{2+} or Mn^{2+} [70]. More recent phylogenomic analysis of the CDF family has seen substrate defined clades provided for Ni²⁺, Cd²⁺ and Co²⁺. While 7 out of 18 identified clades (6 of Zn²⁺ and 1 of Mn²⁺ specificity) agree with the previous system, the Fe^{2+}/Zn^{2+} group was separated into 5 independent clades with Zn^{2+}/Cd^{2+} , Co²⁺/Ni²⁺, Fe²⁺ and Zn²⁺/Cd²⁺/Fe²⁺/Mn²⁺ specificities defined. The new phylogeny for CDFs contains 18 clades including 13 clades with at least one characterized CDF and 5 clades containing only uncharacterized CDFs. Zn²⁺ transporting CDFs are present in 8 of these clades making Zn²⁺ transport polyphyletic. This new grouping of CDFs into defined clades also suggests that Mn²⁺ transport, via CDFs, in eukaryotes and prokaryotes is polyphyletic [17].

Bacterial CDFs are primarily involved in metal tolerance/resistance and homeostasis by efflux of divalent metal cations from the cell. This has been shown for bacteria such as *B. subtilis* [97,103], *Staphylococcus aureus* [111,53], *Escherichia coli* [29,30], *Thermus thermophilus* [96], *Corynebacterium glutamicum* [100], *Deinococcus radiodurans* [98] and *C. metallidurans* [1]. In addition, it has been suggested that bacterial CDFs may be capable of other activity such as mediating antibiotic resistance as is the case of CepA of *Klebsiella pneumoniae* that has been linked to chlorhexidine resistance [23], while two CDFs, MamB and MamM from *Magnetospirillum gryphiswaldense* were recently shown to be involved in magnetosome formation [101]. Interestingly, MamM has been used as a platform for studying CDF-related type II diabetes because of the ease of measurement of its magnetism-related phenotypes [114].

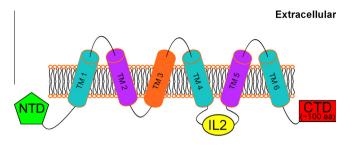
Eukaryotic CDFs are known to have an additional function as intracellular transporters of their substrates. A CDF, termed MSC2, from *Saccharomyces cerevisiae* mediates specific export of ions from the nucleus to the cytoplasm [58], while another two CDFs from *S. cerevisiae*, MMT1 and MMT2, have been suggested to function as mitochondrial Fe²⁺ exporters [57] with evidence of

this export being recently reported [59]. Two further CDFs from the yeast, Zrc1 and Cot1, are responsible for the transport of Zn^{2+} into the vacuole for storage, detoxification and re-use [65,66,69]. A similar function was reported for CDFs from the plants *Arabidopsis thaliana* and *Oryzasativa* L. [52,19,54,68].

Among human CDFs, only ZnT1 is found uniquely in the cell membrane and functions as a Zn²⁺ ions exporter to the extracellular space [113,82]. Other ZnT transporters are localized in the membrane of intracellular organelles to sequester cytoplasmic zinc into various cell compartments such as lysosomes (Znt2; [22]) endosomal/secretory vesicles (ZnT2 and Znt4; [61,78]), synaptic vesicles (Znt3; [14,79]), Golgi apparatus and cytoplasmic vesicles (Znt5, Znt6, Znt7; [51,46,43]) or secretory granules (Znt8; [13]). CDF-2 found in Caenorhabditis elegans was shown to transport zinc ions into gut granules whilst TTM-1B, also from C, elegans, promoted excretion of zinc ions from intestinal cells into the intestinal lumen [85,86]. Certain CDFs have also been shown to function when expressed in other plant or yeast model hosts. The cucumber CDF, CsMTP8, can increase Mn²⁺ tolerance in both S. cerevisiae and A. thaliana. In the yeast it localizes to the vacuolar membrane whilst in A. thaliana it is localized to the protoplast. Similarly, OsMTP8.1, a rice plant CDF, and MTP10 and MTP11 from Beta vulgaris ssp. maritima increases Mn^{2+} tolerance when expressed in S. *cerevisiae* [11,21]. CDF proteins may also function as divalent metal importers when the metal concentration in the cytoplasm is too low. Isoforms of ZnT2 [61] and ZnT5 [102] localized in the plasma membrane were shown to function in both the import and efflux of zinc across the membrane. Similarly, ZAT1p from A. thaliana was found to function as an uptake system in certain situations [7]. More recently, Sll1263, a CDF from the cyanobacterium Synechocystis sp. strain PCC 6803, has been reported to be involved with the import of Fe²⁺ rather than its efflux, possibly due to the low-iron habitats it is associated with the high iron requirements inherent to cyanobacteria [45].

3. Current understanding of signature motifs and metal specificities

Although relatively little is known about the metal specificity of the CDF transporters, there is some evidence for varying sites which can control and influence metal specificity in CDFs. These studies are primarily based on whole cell functional assays and/ or bioinformatics studies. Whilst much of this data has not been validated with more robust in vitro assays, such as reconstitution of purified CDFs into proteoliposomes, the current literature proposes several CDF associated sites of interest. The majority of reports in this regard are focused on plant CDFs, mainly due to the possible role of tailored transporters in biofortification. Bioinformatics studies indicate that the metal specificity of CDFs may reside in the cytoplasmic domain [6] while other studies report that a His-rich loop, known as IL2 (intracellular loop 2), is responsible for metal selectivity [49,81,92]. In AtMTP1 from A. thaliana the sequence within IL2 that restricts the protein to solely Zn²⁺ transport was reduced to the five N-terminal residues of said IL2 [81]. However, residues outside of the cytoplasmic domain and His-rich loop regions have also been shown to influence metal specificity of CDFs which hampers efforts to define a common motif for metal selectivity (Fig. 1). Mutation of two residues (L87H and E97G) within transmembrane helix 3 (TM3) of the S. cerevisiae Zrc1 transporter were found to change metal selectivity completely from Zn²⁺ to Fe²⁺ and Mn²⁺ [60]. Interestingly, homologous residues within TM3 of AtMTP1 (I135F and E145G) were also found to influence metal selectivity, possibly through conformational changes induced at the active site or at the CTD [81]. Homologous residues in YiiP have been shown to be part of an



Intracellular

Fig. 1. Cartoon topology model of a classical prokaryotic CDF. Transmembrane helices (TM) are numbered 1–6, metal specific residues are found in TMs 2 and 5 as part of metal binding site A (purple). Residues predicted to form a hydrophobic gate are found in TM 3 (orange). The N-terminal domain (NTD) is depicted as a green pentagon. The histidine-rich interconnecting loop (IL2) is drawn as a yellow ellipse and the C-terminal domain (CTD) is shown as a red rectangle.

important hydrophobic gate which facilitates Zn²⁺ transport against a stationary proton gradient [33]. Other studies have suggested that the composition of the tetrahedral transport site determines the transport specificity. This tetrahedral transport site, commonly referred to as metal binding site A, is situated in the transmembrane domain of each CDF protomer and is composed of two residues from TM2 and two residues from TM5. The Zn²⁺ and Cd²⁺ specificity of YiiP (FieF) from *E. coli* could be changed to selective Zn²⁺ transport simply by mutation of its DD-HD active site (metal binding site A) to HD-HD, characteristic to mammalian ZnT proteins that transport Zn²⁺ but not Cd²⁺ [40]. Additionally, residue swapping at this position in ZnTs abolished metal selectivity [40]. A single point mutation in TM2 (H90D) of the rice CDF OsMTP1 abolished Zn²⁺ transport but improved Fe²⁺ transport [68]. Moreover, the same study showed that residues located in extracellular loops (ELs) may also play a role in substrate specificity. An L92F mutation in EL1 significantly decreased the affinity to Zn²⁺, enhanced affinity to Fe²⁺ and Co²⁺ and also conferred affinity for Mn²⁺, which is not observed in the wild type protein [68]. As the location of the mutated residues was based on predicted topology of the OsMTP1, it remains to be seen whether ELs have indeed a role in CDF substrate specificity. To add an extra degree of difficulty to pinning down a common motif, CDFs which are found in the same group and share the same tetrahedral binding site can have different metal specificities and these CDFs often do not contain a His-rich loop either. This suggests that there are still further elements outside of the tetrahedral transport site and His-rich loop which govern metal specificity such as TM3 or extracellular loops [18].

4. Variability in size, oligomeric state and transport kinetics – one size does not fit all

Available scientific data indicates that CDF transporters function using an antiport mechanism to export divalent cations. CzcD from *C. metallidurans*, CzcD from *B. subtilis*, two CDF proteins of *E. coli*, ZitB and YiiP (FieF), YiiP from *Shewanella oneidensis*, AtMTP1 from *A. Thaliana* and SmYiiP from *Sinorhizobium meliloti* are driven by the proton motive force [32,56,2,30,49,15,83]. A proton gradient was also required for the function of Zrc1 from *S. cerevisiae* [66] and the transport mediated by human ZnT5 and ZnT1 was also shown to be catalyzed by H⁺/Zn²⁺ exchange [77,93]. CzcD from *B. subtilis* and ZitB from *E. coli* were shown to function utilizing a potassium gradient [32,56]. These results, however, were obtained using whole cell transport assays and later studies with purified and reconstituted ZitB from *E. coli* confirmed the ion efflux catalyzed by this transporter was linked to the import of H^+ ions [9]. While the exchange stoichiometry of metal ions for protons in the case of ZitB was reported to be 1:1, signifying electrogenic antiport [9], CzcD of *B. subtilis* was shown to exchange the divalent cation for two monovalent cations (H^+ or K^+) in an electroneutral process energized by the transmembrane pH gradient [32].

An early phylogenetic analysis of CDFs showed that putative members of the family exhibit an unusual degree of sequence divergence and size variation ranging from 199 to 1677 residues, with the majority of members containing between 300 and 550 amino acids (aa) [26]. Most of the prokaryotic members of the family characterized to date contain approximately 300 amino acids and function as dimers as has been shown for the four proteins for which complete or partial 3D structures are currently known [106.62.12.38.15.115]. The possibility of dimer and homooligomer formation was also demonstrated for a CDF from Salmonella typhi*murium* [27] and plant CDFs [7,5]. Human ZnT proteins have also been shown to form dimers, homodimers of ZnT7 or heterodimers consisting of a monomer of ZnT5 and ZnT6. Those complexes were shown to supply zinc to the secretory pathway by delivering it to alkaline phosphatases [20,99]. Similarly, the two CDF proteins from *M. gryphiswaldense* were shown to form a heterodimer [75,101].

Most of the prokaryotic CDF members possess six transmembrane helices in their integral membrane domain and ~100 aa of their C-terminus form a domain that protrudes into the cytoplasm (CTD). Members of the CDF family often contain the region rich in histidines mentioned earlier which, when present, is located at either terminus or in a cytosolic loop between transmembrane helices 4 and 5 (IL2) (Fig. 1) [35]. The existence of the latter is observed in the Zn²⁺ transporters only and is thought to be involved in metal binding [70,49]. Eukaryotic CDFs are often longer, for example the 724 aa long MSC2 of S. cerevisiae and the 523 aa long human ZTL1, both containing 12 transmembrane helices [58,16], and the 765 aa long human ZnT5 transporter that contains 15 transmembrane helices [46]. It is tempting to speculate that larger members of the family may be able to perform the ion transport in the monomeric form. Indeed, it has been suggested that in the ZnT5/ZnT6 heterodimer, it is the large ZnT5 that is responsible for the zinc transport across the cellular membrane while the ZnT6 part of the heterodimer plays the role of modulator to enhance zinc transporter activity [25].

5. Structure-function analysis of an archetype CDF-YiiP

For many years the CzcD from C. metallidurans was referred to as the archetype of the CDF family. However, it has now been substituted by YiiP from E. coli, since elucidation of its 3D structure in 2007 [62]. The 32.9 kDa, dimeric YiiP resides in the plasma membrane and possesses an 89 aa long C-terminal cytoplasmic domain [106,62]. Early studies indicated that YiiP was involved in the export of Fe²⁺ and hence it was also named FieF (ferrous iron efflux) [30], however, it was confirmed in later studies that YiiP was a very efficient transporter of Zn^{2+} and Cd^{2+} but not Fe^{2+} , Ca²⁺, Co²⁺, Mg²⁺, Mn²⁺ or Ni²⁺ [105]. The X-ray structure of YiiP was initially solved to 3.8 Å resolution [62] and subsequently improved with mercury binding to 2.9 Å [63]. YiiP is a Y-shaped homodimer with the arms formed by transmembrane domains (TMDs) separated from each other by a distance of ~ 20 Å and the stem formed by the C-terminal domains, each linked to the corresponding TMD by an intracellular loop. The six transmembrane helices of the TMD are grouped into two bundles with four (TM1-TM2-TM4-TM5) and two (TM3-TM6) helices. Each YiiP protomer contains three zinc-binding sites (A–C) (Fig. 2) of which only sites A and C are conserved among members of the CDF family. Site A is located roughly in the center of the TMD and constitutes the active site for zinc transport [63,62]. The Zn²⁺ ion in the

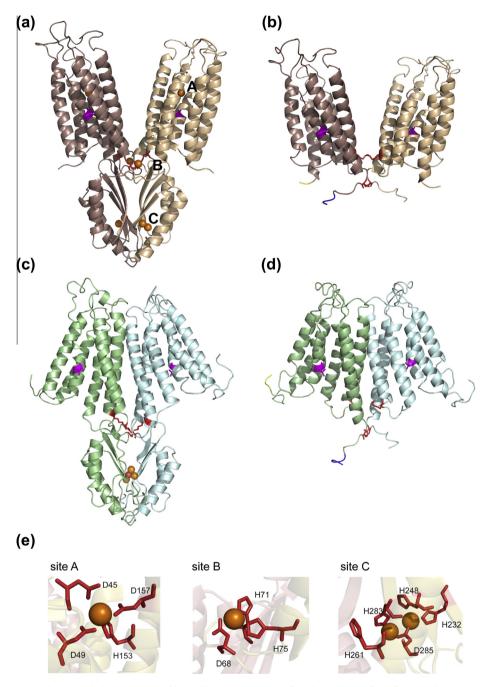


Fig. 2. Comparison between classical and CTD-lacking CDFs. (a and b) – Ribbon representation of the homodimers of YiiP from *E. coli* (PDB ID: 3H90) and from *S. oneidensis* (PDB ID: 3J1Z), respectively. Orange spheres represent zinc ions bound in zinc binding sites A–C that are also indicated. (c and d) – The 3D models of homodimeric CDF3 from *M. maris* built using the *E. coli* and *S. oneidensis* YiiP as the templates, respectively. The models were automatically built using the SUISS-MODEL server [50,3] and include residues 17–206 (c) and 8–206 (d). The N- and C-termini are shown in yellow and blue, respectively. Residues K77 and D207 (YiiP from *E. coli* numbering) and their equivalents in *S. oneidensis* and *M. maris* is shown in magenta. (e) – Coordination of zinc binding sites A–C of YiiP from *E. coli*.

active site is tetrahedrally coordinated by D45 and D49 of TM2 and H153 and D157 of TM5 [63,62]. Such coordination, preferred for Zn²⁺ and Cd²⁺ ions, is in agreement with the ion specificity of YiiP established earlier [105]. The 3D structure of the transporter also revealed an intra- and an extracellular cavity on either side of the membrane. However, although the cavities pointed toward each other in the structure, they did not create a channel across the membrane [62].

Recent studies which used X-ray mediated hydroxyl labeling and mass spectrometry have shown that Zn^{2+} binding in site A triggers a conformational change in the TMD which causes a

rigid-body movement of TM5. This shift in TM5 moves L152 into a position which seals the so-called hydrophobic gate and thus separating these intra- and extracellular cavities. This hydrophobic seal is comprised of six residues: L152 and A149 (TM5), I90 and A83 (TM3), and A194 and M197 from TM6. L152 is the main residue which forms the hydrophobic barrier in this case [33]. The structure is also characterized by four interlocking salt bridges near the membrane surface formed by K77 of TM3 and D207 located in IL3. They provide stabilization of the dimer as well as the orientation of the TM3–TM6 bundle [63]. The binuclear zinc coordination site C of YiiP hosts four Zn²⁺ ions that mediate a tight interaction between CTDs and also stabilize the dimer [63].

6. Proposing a mechanism of action for CDFs

The availability of 3D structures has allowed the development of hypotheses on the mechanism of action of CDFs. In the case of *E. coli* YiiP, although no Zn^{2+} binding was observed within the intracellular cavity of the originally published structure [62], the authors suggested that its existence was possible. Based on this fact, it has been proposed that Zn^{2+} ions could be delivered from the cytoplasm to the intercellular cavity by a putative Zn²⁺ metallochaperone binding to the CTD. Subsequently, the ion would then be translocated across the membrane to the active site toward the bottom of the extracellular cavity [62]. Although zinc delivery to CDFs still remains a mystery, several independent findings support a functional connection between the CTD and the active site A. Site-directed fluorescence resonance energy transfer (FRET) measurements and mutation-activity analysis of YiiP [63] as well as solving the 3D structure of the cytoplasmic domain of the T. thermophilus CDF homolog, CzrB [12], in the presence and absence of Zn²⁺, suggested significant hinge movements of the two electrically repulsive CTDs upon binding of zinc ions that could in turn cause reorientation in the TMD. Moreover, mutation of one of the zinc coordinating residues in site C (H232A) affected the zinc transport in the active site located 49 Å away, thus clearly indicating an allosteric connection between site C and site A [63]. Based on the improved crystal structure of YiiP (2.9 Å vs. 3.8 Å), a mechanism by which YiiP orients itself to allow zinc transport has been proposed (Fig. 3a).

Upon zinc binding, the charge repulsion forces keeping the CTDs apart are overcome and the arms of the cytoplasmic domains are brought closer to each other in a hinge-like manner. They pivot on the charge interlock formed by the four salt bridges situated between the cytoplasmic and integral membrane domains. This charge interlock has been shown to be essential for zinc transport. Upon the inter-CTD movements, the charge interlock in turn alters the TM3–TM6 orientation. Subsequently, TM5 is reoriented due to its packing contact with TM3–TM6 that is otherwise freely suspended in the lipid bilayer. In contrast, because there is little inter-helical contact with TM3–TM6, TM2 remains rather static. The generated shift between TM5 and TM2 was suggested to affect the coordination geometry of the active site and is assumed to create the tetrahedral geometry allowing for zinc transport to occur [63].

A 13 Å cryoelectron microscopy structure of a close YiiP homolog from S. oneidensis provided additional information on the protein mode of action [15]. The structure has been determined in the absence of Zn^{2+} and a model consistent with the obtained electron density map was built using molecular dynamic flexible fitting. The refined model revealed a cytoplasmic-facing state of the protein, as opposed to a periplasmic-facing conformation determined by X-ray crystallography in the presence of Zn²⁺. Upon comparison of the model with the X-ray structure, an alternating access mechanism for zinc transport has been proposed [15] (Fig. 3b). The mechanism proposes that upon zinc binding in the TMD, both transmembrane helical bundles (TM1-TM2-TM4-TM5 and TM3-TM6) pivot around the ion binding sites reaching a periplasmicfacing conformation facilitating Zn²⁺ removal. In the cryo-EM model, additional dimeric interactions within the membrane, at the periplasmic end of TM3 and at the cytoplasmic ends of TM3 and TM6, have been observed. It was postulated that the conformational changes of the monomers may be coordinated by those dimeric interactions and energized by the binding energy of the substrate [15,33]. Moreover, in the cytoplasmic-facing conformation of the protein the intracellular cavity is extended from the cytoplasmic membrane to the Zn^{2+} binding sites [15]. This mechanism of action is further supported by the elucidation of the same well defined channel in apo-YiiP, from site A to the intracellular cavity, in the *E. coli* homolog. The work of Gupta et al. also provides evidence for Zn^{2+} binding at site A facilitating gated access, via L152, to both the intracellular and extracellular cavities which allows for vectorial transport of Zn^{2+} against a stationary proton gradient [33].

7. The cytoplasmic domain of CDFs and controversy over its function

The CDF proteins were initially described as being composed of two main domains [80] and they are still believed to share a twomodular architecture, consisting of a transmembrane domain followed by a C-terminal domain that extends into the cytoplasm. The 3D structures of YiiP from *E. coli* and *S. oneidensis* [62,15] and the structures of the CTDs from T. thermophilus [12], T. maritima [38] and MamM from M. gryphiswaldense [115] demonstrate that CTDs adopt a metallochaperone-like fold, despite the lack of sequence homology. Since metallochaperones carry metal ions to various protein targets in the cytoplasm [76], the CTDs were suggested to play a similar role in sensing the zinc ions and delivering them to the TMD part of the CDF [63,12]. The 92 aa C-terminal domain of T. thermophilus CzrB that begins with a methionine has been independently isolated during phage display while a putative RBS has been localized upstream [96]. This lead to the hypothesis that it may autonomously exist in the cytoplasm and function as a metallochaperone, regulating the activity of the full length CzrB [12]. However, no further evidence has been presented to support this theory. In addition, as the methionine in question is not conserved within the CDF members, this hypothesis, even if true for CzrB, is unlikely to be universally applied within other family members.

The CTDs are proposed to play a crucial role in the scissoring mode of action (Fig. 3a). This mechanism envisages that the otherwise splayed apart monomers of the CTD are brought together upon zinc binding and is supported by FRET measurements performed on YiiP [63] and the crystal structures of the CTD from CzrB [12] in the presence and absence of zinc ions. This drives the further conformational changes in the TMD necessary for zinc transport. In contrast, small angle X-ray scattering (SAXS) and Molecular Dynamics (MD) simulation experiments on MamM demonstrated that its CTD existed as a stable V-shaped dimer even in its apo-form [115]. The characterization of MamM agrees with the work performed on YiiP from E. coli in so far as it also suggested a high degree of natural flexibility in the CTD. This flexibility is thought to be caused by two opposing forces: the charge repulsion between the two negatively charged monomers of the CTD and the opposite attraction caused by hydrophobic interactions at the dimerisation interface which is attempting to pull the monomers together.

Interestingly, Zeytuni et al. also found that, once this flexible apo-CTD bound divalent metal cations, a more closed and stable conformation was achieved. They propose that this movement in the apo-form allowed the CTD to cycle through a number of conformations until the desired metal ion was found. They suggested that there was an additional step which preceded the two-step mechanism which allowed the TMD to facilitate metal transport (Fig. 3b). This initiation step envisages a more stable and compact fold adopted by the CTD once cytoplasmic concentrations reach a certain threshold and subsequently activates the two-step mechanism in the TMD for metal transport [115]. Similarly, the alternative access mechanism portrays the CTD as a static element of

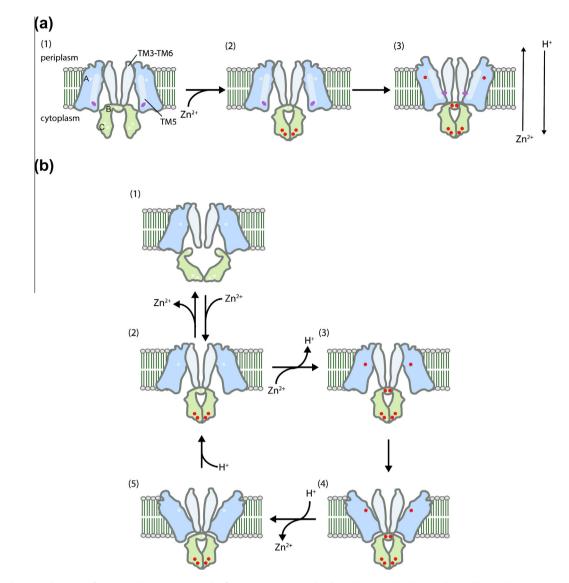


Fig. 3. Proposed CDF mechanisms of action. In the scissoring mode of action (A), upon zinc binding, the two splayed apart electrically repulsive CTDs (green) (1) are brought closer to each other in a hinge-like movement (2). In turn, the orientation of the helices in the TMD (blue) is altered allowing the zinc transport to occur (3; details in the text). In the alternative access mode of action (B) CTDs (green) can exist as a stable V-shaped dimer which is rigid at the bottom vertex in the apo-protein and flexible at the top creating a loose complex capable of searching through conformations for divalent cations (1). Upon zinc binding (2), the CTDs adopt a more compact fold. When the hydrophobic gate between transmembrane helical bundles (blue and light blue) is open to the cytoplasm Zn^{2+} can enter metal binding site A in each protomer (3). Both the transmembrane helical bundles pivot around the ion binding site and reach periplasmic-facing conformation closing the hydrophobic gate to the cytoplasm (4) this facilitates Zn^{2+} removal against a stationary proton gradient (5). The zinc ions are represented by red spheres.

the protein during the conformational changes of its membrane portion. It suggests that Zn²⁺ ions are bound in the zinc binding site C also in the cytoplasmic-facing state of the protein structure which was obtained from crystals grown at low concentration of free zinc ions (below $10 \,\mu\text{M}$) [15]. Limiting the function of these ions only to the structural stabilization of the dimeris in agreement with the fact that the experimental data shows very high affinity of Zn²⁺ binding in site C. Removal of those ions could be achieved by incubation of the protein at high concentrations of EDTA. This led to protein precipitation in the case of two CDF members ZitB from E. coli [9] and YiiP from S. oneidensis [15], suggesting that the presence of Zn²⁺ in site C is essential for protein stability. In contrast, YiiP from E. coli formed dimers even without addition of zinc ions [106], while the CTDs (crystal structures determined in the absence of Zn²⁺), although showing higher flexibility, also existed as dimers [12,38,115]. This evidence lends weight to the presence of a threestep mechanism and the existence of a stable CTD in a Zn²⁺-free form. Polymorphisms in the CTD of a human Znt8 have been associated with the risk of diabetes [95,107] while mutations in the metallochaperone-like domain of P-type ATPases can lead to genetic disorders of copper imbalance [41]. This suggests that the cytoplasmic domain, when present, may function as more than just a stabilizing factor. It is worth mentioning however, that in ZitB from *E. coli* and CzcD from *C. metallidurans* mutants lacking their CTDs and hence the zinc binding site C, have ion transport significantly decreased but not abolished [2]. Interestingly, as the features shown to play an important role in YiiP dimerization, namely the zinc binding site B and the charge interlock forming residues, are present within the TMD of the transporter, we believe it is likely to dimerise even without its CTD.

The CTDs are thought to play an important role in the overall CDF protein function and stability, even if the corresponding theories sometimes do not conform to each other. This already complex picture is further complicated in view of the recent characterization of a functional CDF family member lacking the C-terminal domain [90].

8. Novel, CTD-lacking, subfamily of CDFs

MmCDF3, a putative zinc transporting CDF protein from Maricaulis maris MCS10, has been identified, heterologously produced in E. coli and purified to homogeneity in a dimeric form [90]. It shows ~30% overall sequence similarity to YiiP from E. coli and S. oneidensis concentrated mainly in transmembrane helices and particularly around the active site regions (Fig. 4). Based on its sequence analysis, the protein exhibits some of the typical features of the integral membrane domain of YiiP and other classical CDF proteins such as the number of transmembrane helices (six) and the conserved residues forming the active site (Fig. 4). Interestingly, the two residues responsible for formation of the charge interlock in E. coli (K77 and D207) are also present in MmCDF3 (K77 and D201). While the three Asp residues of the YiiP active site are conserved in MmCDF3, the fourth His is replaced with Cys in MmCDF3. Nonetheless, this should not pose any functional implications in terms of the transport of zinc ions through the integral membrane domain as both residues are known to coordinate zinc. Due to this sequence conservation, the MmCDF3 and other CTD-lacking CDFs (Fig. 5) possess the beginning of the CDF signature reported by Montanini et al. [70].

In contrast to YiiP. MmCDF3 does not contain the zinc binding site B between transmembrane helices TM2 and TM3. Nevertheless, this site is not highly conserved within the CDF family members. This may be a further indicator that the CTD Zn²⁺ ions are not involved in feeding the TMD and are used primarily for stabilization and activation of the TMD for transport. It also strengthens the argument for an alternative access mechanism in CDFs namely because site B is not essential for such a mechanism and divalent metal cations can reach the tetrahedral transport site through the intracellular cavity described earlier. The most prominent difference between the MmCDF3 protein and the archetype of the CDF family is, however, the lack of a CTD. Hence, MmCDF3 also lacks, the otherwise highly conserved, zinc binding site C (Fig. 4). Although the presented differences may question affiliation of this protein to the CDF family, the significantly increased zinc tolerance of the zinc-sensitive E. coli GG48 strain upon complementation with MmCDF3 [89] argues for its genuine role in zinc efflux. Furthermore, the isothermal titration calorimetry (ITC) measurements revealed MmCDF3 being capable of binding zinc and cadmium but not iron and cobalt ions [89]. Interestingly, despite the absence of binding sites B and C, the experimental data confirmed the existence of two binding sites, however, the overall stoichiometry was shown to be lower than that of the classical CDF members such as YiiP from E. coli [10] and Aq_2073 from Aquifex aeolicus [27].

In MmCDF3, the binding site corresponding to the active site A in YiiP binds two Zn^{2+} or Cd^{2+} ions per protein dimer while the additional site is capable of accepting only one ion [89]. While the generated ITC profiles suggested that different residues are involved in binding of Zn^{2+} and Cd^{2+} ions, the competitive binding analysis showed that both ions compete for access at the same sites [89]. The exact location of the additional binding site is to date unknown. However, MmCDF3 exhibits a slightly elongated N-terminus in comparison to the classical members of the family (Fig. 4), suggesting that the additional metal binding site might be located in this region. This hypothesis is supported by the existence of numerous residues, some of them highly conserved in other putative CTD-lacking CDFs that could potentially be involved in zinc coordination (Fig. 5).

As the binding stoichiometry of the additional binding site in MmCDF3 was shown to be one zinc ion per protein dimer, two residues per protomer are most likely involved in the generation of this coordination site. Due to the remarkable conservation within the putative CTD-lacking CDFs, the cysteine residues (C3 and C4, MmCDF3 numbering) would appear to be likely candidates. Moreover, at least two additional potential zinc coordination residues are present in all the analyzed putative CTD-lacking CDFs (Fig. 5). In MmCDF3, one of the two aspartic acids (D7 and D11) situated at the N-terminus, the latter one merits particular attention as it is reasonably conserved within the new subfamily of CDFs (Fig. 5). However, considering the position of the C-termini of those proteins in the generated models (Fig. 2b and d) one cannot exclude their participation in zinc coordination. The C-termini of the protomers are close to each other and are likely to play an important role in the protein dimerization. However, while potential zinc coordinating residues can also be identified in the C-terminal part of MmCDF3, no obvious conservation of these residues is observed, therefore favoring the N-terminus as the terminus harboring the additional metal ion binding site. Although in the generated models the N-termini of the protomers are depicted far apart, the modeling of these flexible regions may not be accurate and it is not complete. It is, therefore, plausible that they are positioned in a manner enabling the coordination of the zinc ion by two protomers. Moreover, lack of the cytoplasmic domain and the intracellular loop between TM2 and TM3 significantly limits the potential for dimerization contacts between the protomers in MmCDF3. As a consequence, the periplasm-facing conformation is unlikely to be achieved without additional stabilization, even in the presence of the charge interlock that is believed to contribute to dimer stabilization in YiiP from E. coli [63]. As the protein exists in solution as a stable dimer, we postulate that the N-termini of the protomers contribute to the protein dimerization that may be further enhanced by zinc binding. Our recent studies have begun to explore the zinc coordinating residues discussed. Point mutations of key residues such as C4A and D7N at the N-terminus and C146A at metal binding site A, have led to significantly decreased zinc tolerance of the zinc-sensitive E. coli GG48 strain upon complementation with MmCDF3 mutants (Noor et al. unpublished results).

9. Possible reasoning for CTD-lacking CDFs

We have identified other putative CTD-lacking CDFs in a number of marine bacteria, some soil bacteria (in particular from the Acinetobacter genus), and certain pathogens from the Haemophilus, Pseudomonas and Pasteurella genera as well as in some bacteria contributing to the nitrogen cycle. Examples of those are presented in the sequence alignment (Fig. 5) and in Table 1. The total number of CDFs in these organisms varies greatly and there is no visible trend between occurrence of the CTD-lacking CDFs and the existence and number of classical CDF members. While most of the CTD-lacking CDFs appear in conjunction with one or more YiiP-like proteins, bacteria, where the truncated transporter constitutes the only CDF protein, also exist. Some marine bacteria even carry more than one CTD-lacking CDF (Table 1). Due to their living environment, marine and saline soil bacteria may have developed transport mechanisms for the active uptake and/or extrusion of numerous ions. Similarly, bacterial pathogens have also evolved elaborate mechanisms which allow them to efficiently compete with their hosts for limiting micronutrients as well as protecting themselves against potentially lethal antimicrobial agents such as copper or mercury [80]. It is reasonable, therefore, to postulate that the presence of the CTD-lacking CDFs is likely to be a part of this mechanism. Taking MmCDF3 as an example for our hypothesis, perhaps some cysteines are required for structural purposes in the form of disulfide bridges, whilst other cysteines may play a role in the transport of Hg^{2+} , Cu^{2+} or other divalent metal cations (Fig. 5). M. maris can grow quite successfully in upwards of 5 µM

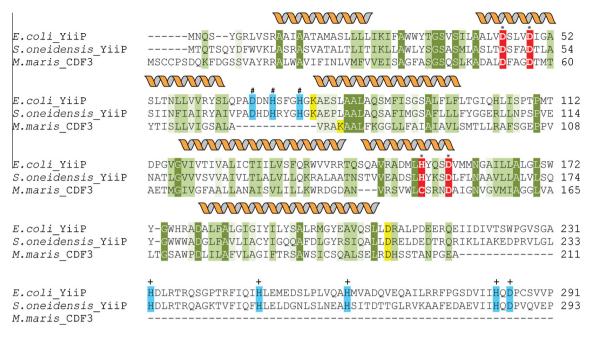


Fig. 4. Sequence alignment of YiiP from *E. coli* and *S. oneidensis* and CTD-lacking CDF from *M. maris*. The alignment was prepared using ClustalW [55,28]. The identical residues are highlighted in dark green; the highly similar and similar residues are highlighted in bright and pale green, respectively. The residues for the conserved active site 'A' are indicated by * and highlighted in red. The residues comprising the zinc binding sites 'B' and 'C' are indicated by # and +, respectively and highlighted in blue. The residues forming the charge interlock are highlighted in yellow. The location of the transmembrane helices in *E. coli* YiiP is indicated on the top of the alignment.

Hg²⁺ and perhaps the presence of short CDFs play a part in this mechanism of resistance [44]. The numerous residues capable of coordination of metal-protein bonds that are found within the N-termini of the new CDF subfamily also support the hypothesis of multiple metal ion transport.

Although MmCDF3 was shown not to transport Fe²⁺ and Co²⁺. this does not necessarily apply to other members of this subfamily. To date no metal binding studies of CTD-lacking CDFs other than MmCDF3 have been reported. In addition, the recent phylogenetic study of CDF transporters originally contained only one CTD-lacking CDF, the Tcr_1855 from marine sulfur oxidizing bacterium Thiomicrospira crunogena XCL-2, that was finally removed from the analysis leaving the current classification of the family without a CTD-lacking representative [17]. It is worth emphasizing that M. maris, and other organisms containing more than one putative CTD-lacking CDF may utilize their alternate CDFs to transport a distinct ion or set of ions. The change in the signature of the active site from DD-HD as found in YiiP to DD-CD in CTD-lacking CDFs may also have implications in metal selectivity as it was described above for several other CDF proteins (Huilan [60,81,68]. Most likely, however, the ion specificity is mediated by several motifs, also outside the active site. This aspect of the CDF transporters is, however, poorly understood and awaits experimental clarification. Recently, another CTD-lacking CDF was demonstrated as taking part in mediation of Pb²⁺ tolerance of a soil bacterium A. xylosoxidans A8 [39]. The signature of its active site (DD-FD) suggests possibly yet another metal specificity. Similar to the proteins presented above, the CTD-lacking CDF from this organism contained a number of potential metal ion coordinating residues on its N-terminus supporting our hypothesis of an additional ion binding site located at the N-terminus of the short CDFs. Mutational or structural analysis are, however, required to confirm this hypothesis. No cysteine residues are present within its N-terminus favoring perhaps conservation of those residues among many CTD-lacking CDFs for metal specificity rather than for formation of disulfide bridges. Classical CDFs contain an entire extra domain thought to play a role in dimerisation, stabilization or, divalent metal cation sensing. It may be that they are more efficient in terms of ion transport and, it is reasonable to speculate that the organisms may express them only in the presence of toxic levels of zinc and other ions that they are capable of transporting. In other situations, perhaps the less efficient but possibly more versatile, in terms of metal transport, CTD-lacking CDFs mediate the ion efflux. In bacteria where only a CTD-lacking CDF is present regulation may primarily be controlled at the gene level. RT-gPCR analysis has demonstrated that many CDF genes are inducible with divalent metal cations. Closely related CDFs have been shown to have varying forms of gene regulation. DmeF from C. metallidurans was shown to be constitutively expressed whereas its homolog DmeF from Rhizobium leguminosarum is induced by nickel and cobalt ions [88]. Some CTD-lacking CDFs may be expressed constitutively in an attempt to continually keep metal concentrations at tolerable levels rather than being expressed in response to toxic metal levels as this stress-induced expression may be energetically unfavorable. Perhaps organisms with only a CTD-lacking CDF adapted to its use because they have lower metal tolerances than organisms with a classical CDF and it is constantly transporting the divalent metal cations rather than being regulated between and active and inactive form by a CTD. It may also be postulated that these less efficient CDFs work together in tandem or series with a not yet identified metal resistance system similar to the RND system. We cannot exclude the possibility that independent proteins play the role of a CTD upon interaction and association with a CTD-lacking CDF. However, it is worth mentioning at this point that to the best of our knowledge there are no clear and obvious homologs to the CTD found in the genomes of bacteria, which possess a CTD-lacking CDF. BLAST searches failed to identify any homologs of a CTD-like protein in organisms containing the classical full length CDFs and the shorter truncated CDFs or just the latter. In organisms which possess both classical and truncated CDFs, only the CTDs of the classical CDFs were returned in BLAST results. An extensive phylogenomic analysis on the CTD-lacking CDFs would be an invaluable resource in understanding the role of these proteins in the host organism. If, however, the homologs of CTDs

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M.maris_CDF3	MSCCPSD-QKFDGSSVAYRRALWAVIFINLVMEVVEISAGFASG <mark>S</mark> QS <mark>I</mark> KADALDFAGD 57
M.maris_CDF2	MS-ASCGHH-QDFDGSAPGFRRALWIVIAINAVMFGVEMLAGAAARSQAUKADALDFAAD 58
H.baltica	
C.litoralis	
P.bermudensis	MS-DCCGPQNFDGASPAYRRVILGIIAINAVMFLVEMAAGFAAQSQAIKADALDFAGD 57
Ruegeria_sp	MA-GCCNHN-ARFDGVSADYKRRIWLVIAINAAMFAVDMGACOMSGSQAFKADALDFLGD 58
R.bacterium	MA-GCCNHD-AKFDGVSDDYKRRIWLVIAINAGMHAVEMGACQMSGSQALKADALDFLGD 58
C.P.marinum	MSSGCCGHD-AQFDGVSDAFKRALWIVIAINGAMFIIPMTAGAFAGSKALQADALDFLGD 59
Silicibacter sp.	OS DCCGP-ONFUGAS PAYRR VILCI IAILAVISLAVISLAVIA PRACECALIVAILA LIFAGU 57 VA-CCCNHD-AKFOGXS DYKRR WILVIAINAANAMAKA COMSCO ALKADALI FLCO 58 VA-CCCNHD-AKFOGXS DYKRR WILVIAINAANEAVISLAVISLAVISLAVISLAVISLAVISLAVISLAVISL
C.salinarum	MAGQCCGAN-ARFDGTSRAYRRVIWAVIAINATMEVVEMAAGLAARSQALQADALDFLGD 59
Roseovarius sp.	MA-GCCGHE-AQFDGLSAAYKORIWIVIALNAAMFGVEMAAGQAAQSQALKABALDFLGD 58
P.gilvum	MG-ACCGHEHGPFDGVSADYRRRLWLVIAINAAMFAVEMGAGOAAGSOALOADALDFLGD 59
Acinetobacter sp.	MOMAGCCHHHEPPKHOTSKFKIAFWIALLINLGWIFFIFVFGCAHIGSTSFWAPALPFLGD 60
A.borkumensis	MGCCDHEIVGNPAPDYQRVLWIVLAINAVMEVVEAASGVLADSRALQADALDFLGD 56
C.psychroerythraea	MS-SCCAAEAKNASERKLLWIVLILNFSMEVIEFIACWLANSSCLLADSLDMLAD 54
I.loihiensis	MS-SCCGTTAQQHIDKAQRTLLWTVLVLNGVMEFVEFIAGWLAESSCLFADSLDMLAD 57
N.oceani	MA-NCCEDKSCEVTALRERHGRVLWIVLIINLVMFFVEGWAGLLAHSTSLLADALDMLGD 59
	VAGCSCDAKHSEDTLKNDRFRRADWIALWINASMEVVEIIAGFNASBASBLADAIDFLGD 59
N.caesariensis	
H.influenzae	MACONCCGSNQP-IHOSPKYKKADWIVLILNLSMEFVBIVMCVKSGSTSDLSDSLDFLGD 59
H.somnus	MACQNCCGSNQP-IHQSPKYKKADWIVLILNLSMFFVBIVMCVKSGSTSELSDSLDFLGD 59
P.multocida	MACQNCCGSNQP-IHQSPKYKKALWIVLILNLSMPFVPIVMGVKSGSTSLLSDSLDFLGD 59
P.stutzeri	MAGNCCSSGCASTAARG-RYRRILWIALLINLAMFGVEIGAGLRSGSVSLLADSLDFFGD 59
A.vinelandii	MPGC-C-TSCSSTPSADPRFRRALWLALFINVAMFALFIGACIKAGSVSLLADAVDFAGD 58
Azoarcus sp.	MPGCSCGSSCAPQTSVSPRFRRAIWVALVINALMEGVELVACLHAGSVSILADAVDFAGD 60
M.maris_CDF3	TMTYTISLLVIGSALAVRAKAALFKGGLLFAIAIAVLSMTLLRAFSGEPPVAETMGIVGF 117
M.maris_CDF2	AATYGLSLYVIGKPARW <mark>RANAAMIKAVSLLAIGISILGLALWRVIFTQQ</mark> EEPALMGSIAV 118
H.baltica	TATWALSLAVIGASVVTRARASLFKGATLALIAISVLIMTVFRVFSGAPFOADTMGLIGF 117
C.litoralis	TAT <mark>YALSLAVIGASVVTRARASLFKGATLALIAISVLIMTVFRVFSGAP</mark> EQADTMGLIGF 117 SVT <mark>YALSLFVIGASLQTRALASLFKAASLGAIALFVLITTALRFFSDAAE</mark> DASTMSLIGC 117
	SATYAISLAVIGSSLVVRARASLFKGATLAVMAMVILALAIGRFFEGTVFEGGTMGAIGF 117
P.bermudensis	SATIATSLAVIGSSLVVRARASLFRGATLAVMAMVILALATGRFFEGIVPEGGIMGATGF 117
Ruegeria sp.	ALTYGISLAVIGATLRTRALAALGKGVSLLLMGIWVFGSTVYQVFYVGV <mark>F</mark> QAEIMGVIGF 118
R.bacterium	ALTYGISLAVIGATLRTRALAALGKGISLLLMGLWVFGSTIYQVFYVGVFQAQIMGLIGF 118
C.P.marinum	TTT <mark>YALSLYVIGMSMRVRATAALLKGFSLAAMGLWVLGSTVYQVLILGI</mark> PSATVMGAVGV 119
Silicibacter sp.	ALTYGISLAVIGASLRTRSMAAIGKGVSLLLMGSWVFGSTVWKVFVVGV <mark>B</mark> EAQVMGYIGF 118
C.salinarum	SATYGISLAVIGMAATVRAKAALVKGISLSIMGLWVLGSTLYRVTVLGTPEAPVMGAIGF 119
Roseovarius sp.	ALTYGLSLAVIGASLRVRATAALFKGLSLMAMGLWVLGSTVYRVIYLGV <mark>B</mark> QAEIMGSIGF 118
P.gilvum	ALTYGLSLAVIGAHLRIRAAAALAKGLSLFAMGAWVLGQTVWRSLYGGVPEPAVMGAVGV 119
Acinetobacter sp.	SINVIISIFALGMSLYWRATVALFKGLTMGLFALIVLGKVLWSYFYGIPPDAITMGIIGL 120
A.borkumensis	TATYGLTLWALGQSVAWRVRAARIKGVSLLLMGVIVLANSIWALVKGSAFQGELMMGVAS 116
C.psychroerythraea	AAVYSLSLYAVGKSLLYKGRAALANGYLQLSLGLLVLVDVARRIWLGSEFQSELMLSIGF 114
I.loihiensis	TLVYAVSLYAVGKAIKYKANAAILNGTLQTVLALVVLADVLQRLIFGSQPNANMMLWVAL 117
N.oceani	ALVYGFSLFVLARSVRWQAGAALAKGGFMLVFGLGVLGEATYKVFYPIMPGVEMMGLIGG 119
N.caesariensis	AANWVISLSVLSMGMLWRSRAALVKGSTMLLFGLFVIAKVVWDFIHGTTEEALTMGAIGF 120
H.influenzae	SAN <mark>W</mark> LISLIVLPMALSYRAKASMVKGLTMGGFGLFILMTTIYRVFYGEMPSYSEISIVGF 119
H.somnus	SANYLISLIVLPMALSYRAKASMVKGLTMGGFGLFILMTTIYRVFYGEMPSYSEMSIVGF 119
P.multocida	SAN <mark>W</mark> LISLIVLPMALSYRAKASMVKGLTMGGFGLFILMTTIYRVFYGEMPSYSEMSIVGF 119
P.stutzeri	AANWGVSLFVLGLGVTMRARASLAKALTMGLFGIFILVVAIGNFVEGSVFHASTMGVVGV 119
A.vinelandii	AANWGISLAVLAMGLTWRARAALVKGLSMAAFGVFVVAKAGWEAFAGIPPEPLTMGVVAV 118
Azoarcus sp.	AANYGISLAVLSLGLAWRSRAALVKGFSMAGYGVFVLGKSVWAAFGGVPPEAMTMGAVAL 120
-	
M.maris_CDF3	AA LANAISVII IKWEDCDANVRSVII SERVAICIVCVMIACGIVAITCSARPELIIA 177
M.maris_CDF3 M.maris_CDF2	AA <mark>LIANAISVLIULKWRDCDANVRSVALCSRND</mark> AIG <mark>NVGVMIAGGLVALTCSAWED</mark> LILA 177 LALLANLASVLIULKWREGDANVRSVALCSRNDAIGNVGVLVAAGLVAWTASPWEDLAVA 178
M.maris_CDF3 M.maris_CDF2 H.baltica	LAFLANLASVLIILRWREGDANVRSVNL <mark>OSRND</mark> AIGNVGVIVAAGLVAWTASPWPDLAVA 178 AAFLANLTSVAILIKWRDGDSNVRSVNLOSRNDAIGNVAVILAAFAVAYTNTAWPDLIVA 177
M.maris_CDF3 M.maris_CDF2 H.baltica C.litoralis	LAILARLASULITLRWREGDANVRSV <mark>RL</mark> GERNDAIG <mark>W</mark> UGVUVAGLUAWTASPWPDLAVA 177 AAJLANLTSVAIIIKWRDGDSNVRSVMLGERNDAIGWUAVILAAFAVAYINTAWPDLIVA 177 IALLAVASVFILLRWRDGDSNVRSVMLGERNDAIGWUGVIAAGFLVSATGSAWEDLEVG 177
M.maris_CDF3 M.maris_CDF2 H.baltica	LAILAALASVIJIIJRWREGDANVRSVALOSRADAIGNGVIVAAGLVAWTASPWPDLAVA 178 AALAALTSVAIIIKKRDGDSNVRSVALOSRADAIGNVAVILAAFAVAYINTAWPDLIVA 177 IALLAAVASVFILLRWRDGDSNVRSVALOSRADAIGNGVIAAGFLVSATGSAWPDLFVG 177 LAPAALASLFILLRWREGDANVRSVALOSRADAIGNVGVIMAAGLVKLTGSAWPDLIMA 177
M.maris_CDF3 M.maris_CDF2 H.baltica C.litoralis	LAILARLASVLIITURWIRGCDANVRSVOLSENDAIC VGVIVAACLAWTASPWPDLAVA 17 AAPLARITSVAITIKWEDGDSNVRSVOLSENDAIC VVAVILARAFVAVINTAMPULIVA 17 IAPLANVASVFIJLRWRDGDSNVRSVOLSENDAIG VGVIAAGFLVSATGSAMPDLFVG 177 LAPAANLASIFIJLRWREDGANVRSVOLSENDAAC VGVIMAACLVKLTGSAWPDLFVA 178 MALAANLISVMLIARVKDGDANVRSVOLSENDAAC VGVIMAACLVKLTGSAWPDLFVA 178
M.maris_CDF3 M.maris_CDF2 H.baltica C.litoralis P.bermudensis	LAILANLLSVLIILURWIKEGDANVRSVNLSERNDAIG VGVIVAAGLAWTASPWPDLAVA 177 AADLANLTSVAILIKWRDGDSNVRSVNLSERNDAIG VGVILAAFAVAYTNTAWPDLIVA 177 IAPLAAVASVFITURWRDGDSNVRSVNLSERNDAIG VGVIAAGFLVSATGSAWPDLIVA 177 LAIAATLASEFTURWREGDANVRSVNLSERNDAAG VGVIMAAGLVKLTGSAWPDLIMA 177 MAIAANLISVMLIARYKDGDANVRSVNLSERNDAIG VGVIMAAGLVKLTGSAWPDLIMA 177 MAPAALISVMLIARYKDGDANVRSVNLSERNDAIG VGVIMAAGLVKLTGSAWPDLIMA 178 MAPAALISVLLIARYKDGDANVRSVNLSERNDAIG VGVIMAAGLVKTGVFTUVA 178
M.maris_CDF3 M.maris_CDF2 H.baltica C.litoralis P.bermudensis Ruegeria sp.	LAILARLASVLIITURWIRGCDANVRSVOLSENDAIC VGVIVAACLAWTASPWPDLAVA 17 AAPLARITSVAITIKWEDGDSNVRSVOLSENDAIC VVAVILARAFVAVINTAMPULIVA 17 IAPLANVASVFIJLRWRDGDSNVRSVOLSENDAIG VGVIAAGFLVSATGSAMPDLFVG 177 LAPAANLASIFIJLRWREDGANVRSVOLSENDAAC VGVIMAACLVKLTGSAWPDLFVA 178 MALAANLISVMLIARVKDGDANVRSVOLSENDAAC VGVIMAACLVKLTGSAWPDLFVA 178
M.maris_CDF3 M.maris_CDF2 H.baltica C.litoralis P.bernudensis Ruegeria sp. R.bacterium C.P.marinum	LA LARLASVLITILRWREGDANVRSVRLSERNDATG WGVTUVAAGLAWTASPWPDLAVA 178 AAD LANLTSVATTILRWREGDANVRSVRLSERNDATG WGVTUVAAGLAWTASPWPDLAVA 177 IAD LANVASVFTTILRWREDGDSNVRSVNLSERNDATG WGVTAAGFLVSATGSAWPDLIVA 177 LAVAACLASEFTTILRWREDGDSNVRSVNLSERNDATG WGVTAAGAUSTGSAWPDLIVA 170 MATAACLISVLILLRWREDGDANVRSVNLSERNDATG WGVTATGAWPDLIVA 178 MAJAACLISVLILARVREDGDANVRSVNLSERNDATG WAVMIAALGVWGTATGAWPDLIVA 178 LAVACLISVLIJARVREDGDANVRSVNLSERNDATG WAVMIAALGVWGTATGAWPDLIVA 178 LAVACLISVLIJARVREDGDANVRSVNLSERNDATG WAVMIAALGVWGTATGAWPDLIVA 178 LAVACLISVLIJARVREDGDANVRSVNLSERNDATG WAVMIAALGVWGTATGAWPLIVA 178 LAVACUSVLIJARVREDGDANVRSVLSERNDATG WAVMIAALGVWGTATGAWPLIVA 178
M.maris_CDF3 M.maris_CDF2 H.baltica C.litoralis P.bermudensis Ruegeria sp. R.bacterium C.P.marinum Silicibacter sp.	LA LARLASVLITILRWREGDANVRSVRLSERNDATG WGVTUVAAGLAWTASPWPDLAVA 178 AAD LANLTSVATTILRWREGDANVRSVRLSERNDATG WGVTUVAAGLAWTASPWPDLAVA 177 IAD LANVASVFTTILRWREDGDSNVRSVNLSERNDATG WGVTAAGFLVSATGSAWPDLIVA 177 LAVAACLASEFTTILRWREDGDSNVRSVNLSERNDATG WGVTAAGAUSTGSAWPDLIVA 170 MATAACLISVLILLRWREDGDANVRSVNLSERNDATG WGVTATGAWPDLIVA 178 MAJAACLISVLILARVREDGDANVRSVNLSERNDATG WAVMIAALGVWGTATGAWPDLIVA 178 LAVACLISVLIJARVREDGDANVRSVNLSERNDATG WAVMIAALGVWGTATGAWPDLIVA 178 LAVACLISVLIJARVREDGDANVRSVNLSERNDATG WAVMIAALGVWGTATGAWPDLIVA 178 LAVACLISVLIJARVREDGDANVRSVNLSERNDATG WAVMIAALGVWGTATGAWPLIVA 178 LAVACUSVLIJARVREDGDANVRSVLSERNDATG WAVMIAALGVWGTATGAWPLIVA 178
M.maris_CDF3 M.maris_CDF2 H.baltiCa C.litoralis P.bernudensis Ruegeria sp. R.bacterium C.P.marinum Silicibacter sp. C.salinarum	LA LARLASVLITURWREGDANVRSVLSERNDATG VGVUVAAGLAWTASPW PDLAVA 178 AAP LARLTSVATTURWREGDANVRSVLSERNDATG VGVUVAAGLAWTASPW PDLAVA 177 TAPLANVASVFTULRWREGDSNVRSVLSERNDATG VGVTAAGELVSATGSAWPDLIVA 177 AAA LASLEFLURWREGDANVRSVLSERNDATG VGVTAAGELVSATGSAWPDLIVA 178 MAPAARLISVLIARVKDGDANVRSVLSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 MAPAARLISVLJARVKDGDANVRSVLSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 MAPAARLISVLIARVKDGDANVRSVLSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 MAPAARLISVLIARVKDGDANVRSVLSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 MAPAARLISVLIARVKDGDANVRSVLSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 MAPAARLISVLIARVKDGDANVRSVLSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 MAPAARLISVLIARVKDGDANVRSVLSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 MAPAARLISVLIARVKDGDANVRSVLSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 MAPAARLISVLIARVKDGDANVRSVLSERNDATG VAVMTAALGVWGTATGWPDLIVA 178
M.maris_CDF3 M.maris_CDF2 H.baltica C.litoralis P.bermudensis Ruegeria sp. R.bacterium C.P.marinum Silicibactor sp. C.salinarum Roseovarius sp.	LA LARLASVLITURWREGDANVRSVLSERNDATG VGVUVAAGLAWTASPW PDLAVA 178 AAP LARLTSVATTURWREGDANVRSVLSERNDATG VGVUVAAGLAWTASPW PDLAVA 177 TAPLANVASVFTULRWREGDSNVRSVLSERNDATG VGVTAAGELVSATGSAWPDLIVA 177 AAA LASLEFLURWREGDANVRSVLSERNDATG VGVTAAGELVSATGSAWPDLIVA 178 MAPAARLISVLIARVKDGDANVRSVLSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 MAPAARLISVLJARVKDGDANVRSVLSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 MAPAARLISVLIARVKDGDANVRSVLSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 MAPAARLISVLIARVKDGDANVRSVLSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 MAPAARLISVLIARVKDGDANVRSVLSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 MAPAARLISVLIARVKDGDANVRSVLSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 MAPAARLISVLIARVKDGDANVRSVLSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 MAPAARLISVLIARVKDGDANVRSVLSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 MAPAARLISVLIARVKDGDANVRSVLSERNDATG VAVMTAALGVWGTATGWPDLIVA 178
M.maris_CDF3 M.maris_CDF2 H.baltLca C.litoralis P.bernudensis Ruegeria sp. R.bacterium C.P.marinum Silicibactor sp. C.salinarum Roseovarius sp. P.gilvum	LA LARLASVLITURWREGDANVRSVELSERNDATG VGVUVAAGLAWTASPWPCLAVA 177 AAD LANLTSVATTIRWRDGDSNVRSVELSERNDATG VGVUVAAGLAWTASPWPCLAVA 177 TAPLANVASVFTTURWRDGDSNVRSVMLSERNDATG VGVIAAFAVAYTNTAMEDLIVA 177 LAPANCASFFTTURWRDGDSNVRSVMLSERNDATG VGVIMAAGLVSATGSAWEDLIVA 177 MATAALISVLILWRDGDANVRSV LSERNDATG VGVIMAAGLVKITGSAWEDLIVA 178 MATAALISVLIJARYKDGDANVRSV LSERNDATG VGVIMAAGLVKUTGATGSWEDLIVA 178 LAPTANLISVLIJARYKDGDANVRSV LSERNDATG VAVMIAALGVWGTATGSWEDLIVA 178 LAPTANLISVLIJARYKDGDANVRSV LSERNDATG VAVMIAALGVWGTATGSWEDLIVA 178 LAPTANLISVLIJWRRKDGDANVRSV LSERNDATG VAVMIAALGVWGTATGSWEDLIVA 178 LAPTANLISVLIJWRRNGDANVRSV LSERNDATG VAVMIAALGVWGTATGSWEDLIVA 178 LAPTANLISVLIJWRRNGDANVRSV LSERNDATG VAVMIAALGVWGTATGSWEDLIVA 178 LAPTANLISVLIJWRRNGDANVRSV LSERNDATG VAVMIAALGVWGTATGSWEDLIVA 179 LAPAAVASVLIJWRRNGDANVRSV LSERNDATG VAVMVAALAVWGTETGSWEDLIVA 179 LAPAAVASVLIJWRRKDGDANVRSV LSERNDATG VAVMVAALGVWGTATGSWEDLIVA 179 LAPAAVASVLIJWRRKDGDANVRSV LSERNDATG VAVMVAALGVWGTASGEDGVEDLIVA 179
M.maris_CDF3 M.maris_CDF2 H.baltica C.litoralis P.bernudensis Ruegeria sp. R.bacterium C.P.marinum Silicibactor sp. C.salinarum Roseovarius sp. P.gilvum Acinetobacter sp.	LA LARLASVLII TURWIRGOANVRSVGLÜSIRNDAIG VGVIVAAGLVAWTASPWPDLAVA 178 AARLAGUTSVAIT TURWIGOBONVRSVGLÜSIRNDAIG VGVVILAAFAVAYINTAMPUTUVA IARLAGUSVAITAVANDOGONVRSVGLÜSIRNDAIG VGVIAAGELVSATGSAMPDLIVA 177 IARLAGUSVELIAURVREGONVRSVGLÜSIRNDAIG VGVIAAGELVSATGSAMPDLIVA 178 MARLAGUSVELIAURVREGONVRSVGLÜSIRNDAIG VGVIAAGELVSATGSAMPDLIVA 178 MARLAGUSVELIARVKDEGANVRSVGLÜSIRNDAIG VANNIAALGVWGTATGWPDLIVA 178 MARLAGUSVELIARVKDEGANVRSVGLÜSIRNDAIG VANNIAALGVWGTATGWPDLIVA 178 MARLAGUSVELIARVKDEGANVRSVGLÜSIRNDAIG VANNIAALGVWGTATGWPDLIVA 179 MARLAGUSVELUNGVREGODANVRSVGLÜSIRNDAIG VANNIAALGVWGTATGWPDLIVA 179 MARLAGUSVELUNGVREGODANVRSVGLÜSIRNDAIG VANNIAALGVWGTATGWPDLIVA 179 MARLAGUSVELUNGVREGODANVRSVGLÜSIRNDAIG VANNIAALGVWGTATGWPDLIVA 179 LAMLAGVASVLILMRWRNGDANVRSVGLÜSIRNDAIG VANNIAALGVWGTATGWPDLIVA 178 LAMLAGVASVLILMRWRNGDANVRSVGLÜSIRNDAIG VANNVAALGVWGTETGWPDLIVA 178 LAMLAGVASVLILMRKKNEGDANVRSVGLÜSIRNDAIG VANNVAALGVWGTETGWPDLIVA 178 LAMLAGVASVLILMRKKNEGDANVRSVGLÜSINDAIG VANNVAALGVWGTETGWPDLIVA 178 LAMLAGVASVLILMRKKNEGDANVRSVGLÜSINDAIG VANNVAALGVWGTETGWPDLIVA 178 LAMLAGVSULUMRKKNEGDANVRSVGLÜSINDAIG VANNVAALGVWGTETGWPDLIVA 178 LAMLAGVSULUMRKKNEGDANVRSVGLÜSINDAIG VANNVAALGVWGTETGWPDLIVA 178 LAMLAGVSULUMRKKNEGDANVRSVGLÜSINDAIG VANNVAALGVWGTETGWPDLIVA 178 LAMLAGVSULUMRKKNEGDANVRSVGLÜSINDAIG VANNVAALGVWGTETGWPDLIVA 180
M.maris_CDF3 M.maris_CDF2 H.baltLca C.litoralis P.bermudensis Ruegeria sp. R.bacterium C.P.marinum Silicibactor sp. C.salinarum Roseovarius sp. P.gilvum Acinetobacter sp. A.borkumensis	LA LARLASVLITILRWREGDANVRSVGLSERNDATG VGVTVAAGLVAWTASPWPDLAVA 178 AAP LARLTSVAITIKWROGDSNVSSVLGSERNDATG VGVTVAAGTVAWTNASPWPDLAVA 177 TAP LANVASVFTDLRWRDGDSNVSSVLGSERNDATG VGVTAAGFLVSATGSAWPDLFVG 177 LAPAALASTEDLJRWREGDANVRSVLGSERNDATG VGVTAAGFLVSATGSAWPDLFVG 177 MAP AARLISVNLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLVVA 178 MAP AARLISVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 MAP AARLISVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 LAPTALLSVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 LAPTALLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTALLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTARLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTARVSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTAGSGVPDLIVA 178 LAPTARVSVLIMRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTAGSGVPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGSGVPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGTSGPLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGTSGPLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGTSGPLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGTGEDFDLIVA 178 LAPARVASULLBRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGTGEDFDLIVA 178 LAPARVSULLBRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGTGEDFDLIVA 178 LAPARVASULLBRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGELDVDLOGLIVA 170 LAPARVASULLBRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGLSGVDLIVA 170 LAPARVASULLBRVRDDANVRSVLGSERNDATG VAVMVAALGVWGTGELDVDLIVA 170 LAPARVASULLBRVRDDANVRSVLGSERNDATG VAVMVAALGVWGTGELDVDLOGLIVA 170 LAPARVASULFARVEDDANVRSVLGSERNDATG VAVMVAALGVWAALGVWGTGUNGTGELUVA
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M.maris_CDF3 M.maris_CDF2 H.baltica C.litoralis P.bermudensis Ruegeria sp. R.bacterium C.P.marinum Silicibactor sp. C.salinarum Roseovarius sp. P.gilvum Acinetobacter sp. A.borkumensis C.psychroerythraea I.loihiensis	LA LARLASVLITILRWREGDANVRSVGLSERNDATG VGVTVAAGLVAWTASPWPDLAVA 178 AAP LARLTSVAITIKWROGDSNVSSVLGSERNDATG VGVTVAAGTVAWTNASPWPDLAVA 177 TAP LANVASVFTDLRWRDGDSNVSSVLGSERNDATG VGVTAAGFLVSATGSAWPDLFVG 177 LAPAALASTEDLJRWREGDANVRSVLGSERNDATG VGVTAAGFLVSATGSAWPDLFVG 177 MAP AARLISVNLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLVVA 178 MAP AARLISVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 MAP AARLISVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 LAPTALLSVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 LAPTALLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTALLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTARLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTARVSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTAGSGVPDLIVA 178 LAPTARVSVLIMRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTAGSGVPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGSGVPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGTSGPLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGTSGPLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGTSGPLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGTGEDFDLIVA 178 LAPARVASULLBRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGTGEDFDLIVA 178 LAPARVSULLBRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGTGEDFDLIVA 178 LAPARVASULLBRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGELDVDLOGLIVA 170 LAPARVASULLBRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGLSGVDLIVA 170 LAPARVASULLBRVRDDANVRSVLGSERNDATG VAVMVAALGVWGTGELDVDLIVA 170 LAPARVASULLBRVRDDANVRSVLGSERNDATG VAVMVAALGVWGTGELDVDLOGLIVA 170 LAPARVASULFARVEDDANVRSVLGSERNDATG VAVMVAALGVWAALGVWGTGUNGTGELUVA
M.maris_CDF3 M.maris_CDF2 H.baltiCa C.litoralis P.bermudensis Ruegeria sp. R.bacterium C.P.marinum Sillcibacter sp. C.salinarum Roseovarius sp. P.gilvum Acinetobacter sp. A.borkumensis C.psychroerythraea I.loihiensis N.oceani	LA LARLASVLITILRWREGDANVRSVGLSERNDATG VGVTVAAGLVAWTASPWPDLAVA 178 AAP LARLTSVAITIKWROGDSNVSSVLGSERNDATG VGVTVAAGTVAWTNASPWPDLAVA 177 TAP LANVASVFTDLRWRDGDSNVSSVLGSERNDATG VGVTAAGFLVSATGSAWPDLFVG 177 LAPAALASTEDLJRWREGDANVRSVLGSERNDATG VGVTAAGFLVSATGSAWPDLFVG 177 MAP AARLISVNLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLVVA 178 MAP AARLISVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 MAP AARLISVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 LAPTALLSVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 LAPTALLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTALLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTARLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTARVSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTAGSGVPDLIVA 178 LAPTARVSVLIMRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTAGSGVPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGSGVPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGTSGPLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGTSGPLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGTSGPLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGTGEDFDLIVA 178 LAPARVASULLBRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGTGEDFDLIVA 178 LAPARVSULLBRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGTGEDFDLIVA 178 LAPARVASULLBRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGELDVDLOGLIVA 170 LAPARVASULLBRVRDGDANVRSVLGSERNDATG VAVMVAALGVWGTGLSGVDLIVA 170 LAPARVASULLBRVRDDANVRSVLGSERNDATG VAVMVAALGVWGTGELDVDLIVA 170 LAPARVASULLBRVRDDANVRSVLGSERNDATG VAVMVAALGVWGTGELDVDLOGLIVA 170 LAPARVASULFARVEDDANVRSVLGSERNDATG VAVMVAALGVWAALGVWGTGUNGTGELUVA
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M.maris_CDF3 M.maris_CDF2 H.baltiCa C.litoralis P.bermudensis Ruegeria sp. R.bacterium C.P.marinum Silicibactor sp. C.salinarum Roseovarius sp. P.gilvum Acinetobacter sp. A.borkumensis C.psychroerythraea I.loihiensis N.oceani N.caesariensis H.influenzae H.somuus	LA LARLASVLITILRWREGDANVRSVGLSERNDATG VGVTVAAGLVAWTASPWPDLAVA 178 AAP LARLTSVAITIKWROGDSNVSSVLGSERNDATG VGVTVAAGTVAWTNASPWPDLAVA 177 TAP LANVASVFTDLRWRDGDSNVSSVLGSERNDATG VGVTAAGFLVSATGSAWPDLFVG 177 LAPAALLASTEDLJRWREGDANVRSVLGSERNDATG VGVTAAGFLVSATGSAWPDLFVG 177 MAP AARLISVNLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLVVA 178 MAP AARLISVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 MAP AARLISVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 LAPTALLSVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 LAPTALLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTALLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTARLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTARVSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTAGSCWPDLIVA 178 LAPTARVSVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTAGSCWPDLIVA 178 LAPARVSVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTGTSWPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTGTSWPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTGTSWPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTGTSWPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 178 LAPARVASVLIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGUPDLIVA 174 LAPARVASULIMAVEDDANVRSVLGSERNDATG VAVMVALGVWGTGUPDLIVA
M.maris_CDF3 M.maris_CDF3 H.baltLca C.litoralis P.bernudensis Ruegeria sp. R.bacterium C.P.marinum Silicibactor sp. C.salinarum Roseovarius sp. P.gilvum Acinetobacter sp. A.borkumensis C.psychroerythraea I.loihiensis N.caesariensis H.influenzae H.somnus P.multocida	LA LARLASVLITILRWREGDANVRSVGLSERNDATG VGVTVAAGLVAWTASPWPDLAVA 178 AAP LARLTSVAITIKWROGDSNVSSVLGSERNDATG VGVTVAAGTVAWTNASPWPDLAVA 177 TAP LANVASVFTDLRWRDGDSNVSSVLGSERNDATG VGVTAAGFLVSATGSAWPDLFVG 177 LAPAALLASTEDLJRWREGDANVRSVLGSERNDATG VGVTAAGFLVSATGSAWPDLFVG 177 MAP AARLISVNLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLVVA 178 MAP AARLISVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 MAP AARLISVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 LAPTALLSVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 LAPTALLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTALLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTARLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTARVSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTAGSCWPDLIVA 178 LAPTARVSVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTAGSCWPDLIVA 178 LAPARVSVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTGTSWPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTGTSWPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTGTSWPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTGTSWPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 178 LAPARVASVLIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGUPDLIVA 174 LAPARVASULIMAVEDDANVRSVLGSERNDATG VAVMVALGVWGTGUPDLIVA
M.maris_CDF3 M.maris_CDF2 H.baltiCa C.litoralis P.bermudensis Ruegeria sp. R.bacterium C.P.marinum Sillcibacter sp. C.salinarum Roseovarius sp. P.gilvum Acinetobacter sp. A.borkumensis C.psychroerythraea I.loihiensis N.oceani N.oceani N.oceani H.influenzae H.somnus P.multocida P.stutzeri	LA LARLASVLITILRWREGDANVRSVGLSERNDATG VGVTVAAGLVAWTASPWPDLAVA 178 AAP LARLTSVAITIKWROGDSNVSSVLGSERNDATG VGVTVAAGTVAWTNASPWPDLAVA 177 TAP LANVASVFTDLRWRDGDSNVSSVLGSERNDATG VGVTAAGFLVSATGSAWPDLFVG 177 LAPAALLASTEDLJRWREGDANVRSVLGSERNDATG VGVTAAGFLVSATGSAWPDLFVG 177 MAP AARLISVNLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLVVA 178 MAP AARLISVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 MAP AARLISVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 LAPTALLSVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 LAPTALLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTALLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTARLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTARVSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTAGSCWPDLIVA 178 LAPTARVSVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTAGSCWPDLIVA 178 LAPARVSVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTGTSWPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTGTSWPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTGTSWPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTGTSWPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 178 LAPARVASVLIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGUPDLIVA 174 LAPARVASULIMAVEDDANVRSVLGSERNDATG VAVMVALGVWGTGUPDLIVA
M.maris_CDF3 M.maris_CDF2 H.baltiCa C.litoralis P.bermudensis Ruegeria sp. R.bacterium C.P.marinum Sillcibacter sp. C.salinarum Roseovarius sp. P.gilvum Acinetobacter sp. A.borkumensis C.psychroerythraea I.loihiensis N.oceani N.oceani N.oceani H.influenzae H.somnus P.multocida P.stutzeri	LA LARLASVLITILRWREGDANVRSVGLÜSENDATG VGVUVAAGLVAWTASPWEDLAVA 178 AAR LARLTSVALTIEWRDGDSNVRSVGLÜSENDATG VGVIDAAGLVAWTASPWEDLAVA 177 TAPLAAVASVFTDLRWRDGDSNVRSVGLÜSENDATG VGVIDAAGLVSATGSAWEDLFVG 177 LAPAAN LASEFLUEWRREGDANVRSVGLÜSENDATG VGVIDAAGLVSATGSAWEDLFVG 177 MAR AARLISVULIARVKDGDANVRSVGLÜSENDATG VGVIDAAGLVSATGSAWEDLFVA 178 MAR AARLISVLIARVKDGDANVRSVGLÜSENDATG VAVMITALGVWGTATGWEDLTVA 178 LAPTANLISVFLUARVKDGDANVRSVGLÜSENDATG VAVMITALGVWGTATGWEDLTVA 179 MAR AARLISVLIARVKDGDANVRSVGLÜSENDATG VAVMITALGVWGTATGWEDLTVA 179 LAPTANLISVLIMRFKDGDANVRSVGLÜSENDATG VAVMITALGVWGTATGWEDLTVA 179 LAPTANLISVLIMRFKDGDANVRSVGLÜSENDATG VAVMITALGVWGTATGWEDLTVA 179 MAR AARLUSVLIMRFKDGDANVRSVGLÜSENDATG VAVMITALGVWGTATGWEDLTVA 178 LAPTANLISVLIMRFKDGDANVRSVGLÜSENDATG VAVMITAAGGVWATGTGWEDTUVA 178 LAPTANGVLUFFRVFDGDANVRSVGLÜSENDATG VAVMITAAGGVWATGTSVEDLTVA 179 LAPTANGVSVLIPRVFDGDANVRSVGLÜSENDATG VAVMITAAGGVWATGTSVEDLTVA 179 LAPTANGVSVLIPRVFDGDANVRSVGLÜSENDATG VAVMITAAGGVWATGTSVEDLTVA 179 LAPTANGVSVLIPRVFDGDANVRSVLÜSENDATG VAVMITAAGGVWATGTSVEDLTVA 179 LAPTANGVSVLIPRVFDGDANVRSVLÜSENDATG VAVMITAAGGVWATGTSVEDLTVA 179 LAPTANGVSVLIPRVFDGDANVRSVLÜSENDATG VAVMITAAGGVWATGTSVEDLTVA 179 LAPTANGVSVLIPRVFDGDANVRSVLÜSENDATG VAVMITAAGSVERTGVEDTUVA 179 LAPTANGVSVLIPRVFDGDANVRSVLÜSENDATG VAVMITAAGSVERTGVEDTUVA 179 LAPTANGVSVLIPRVFDGDANVRSVLÜSENDATG VAVMITAAGSVERTGVEDTUVA 179 LAPTANGVSVLIPRVFDGDANVRSVLÜSENDATG VAVMITAAGSVERTGVEDTUVA 179 LAPTANGVSVLIPRVFDGDANVRSVLÜSENDATG VAVMITAAGSVERTGVEDTUVA 179 LAPTANGVSVLIPRVFDGDANVRSVLÜSENDATG VAVMITAAGSVERTGVEDTUVA 179
M.maris_CDF3 M.maris_CDF2 H.baltiCa C.litoralis P.bermudensis Ruegeria sp. R.bacterium C.P.marinum Sillcibacter sp. C.salinarum Roseovarius sp. P.gilvum Acinetobacter sp. A.borkumensis C.psychroerythraea I.loihiensis N.oceani N.oceani N.oceani H.influenzae H.somnus P.multocida P.stutzeri	LA LARLASVLITILRWREGDANVRSVGLSERNDATG VGVTVAAGLVAWTASPWPDLAVA 178 AAP LARLTSVAITIKWROGDSNVSSVLGSERNDATG VGVTVAAGTVAWTNASPWPDLAVA 177 TAP LANVASVFTDLRWRDGDSNVSSVLGSERNDATG VGVTAAGFLVSATGSAWPDLFVG 177 LAPAALLASTEDLJRWREGDANVRSVLGSERNDATG VGVTAAGFLVSATGSAWPDLFVG 177 MAP AARLISVNLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLVVA 178 MAP AARLISVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 MAP AARLISVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 LAPTALLSVLIARVKDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 179 LAPTALLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTALLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTARLSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTATGWPDLIVA 178 LAPTARVSVLIMRVRDGDANVRSVLGSERNDATG VAVMTAALGVWGTAGSCWPDLIVA 178 LAPTARVSVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTAGSCWPDLIVA 178 LAPARVSVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTGTSWPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTGTSWPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTGTSWPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTGTSWPDLIVA 178 LAPARVASVLIMRVRDGDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 178 LAPARVASVLIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTSUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGTUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGUPDLIVA 174 LAPARVASULIMRVRDDANVRSVLGSERNDATG VAVMVALGVWGTGUPDLIVA 174 LAPARVASULIMAVEDDANVRSVLGSERNDATG VAVMVALGVWGTGUPDLIVA
M.maris_CDF3 M.maris_CDF2 H.baltLGa C.litoralis P.bermudensis Ruegeria sp. R.bacterium C.P.marinum Sillcibactor sp. C.salinarum Roseovarius sp. P.gilvum Acinetobacter sp. A.borkumensis C.psychroerythraea I.loihiensis N.oceani N.oceasi H.influenzae H.sonnus P.multocida P.stutzeri A.vinelandii Azoarcus sp.	LA ILA LASULTI TURNEGOANNESY LOSINDATG YGYTYAAGLYAWTASPR POLAYA 178 AAP LAQ ITSYATI TURNEGOSNIKSY LOSINDATG YGYTAAGTYAATYNTAK PUTLYA 177 IAD AALASYFTI TURNEGOSNIKSY LOSINDATG YGYTAAGTYSATGYPOLIYA 177 IAD AALASYFTI TURNEGOSNIKSY LOSINDATG YGYTAAGTYSATGYPOLIYA 177 IAD AALLSYNLI TURNEGOANNESY LOSINDATG YGYTAAGTYSTIC 187 MAD AALTSYTLI REKEGOANNESY LOSINDATG YAYMTAALGWGTATGYPOLIYA 178 MAD AALTSYLLI ARKKOCDANNESY LOSINDATG YAYMTAALGWGTATGYPOLIYA 179 MA AALLSYNLI ARKKOCDANNESY LOSINDATG YAYMTAALGWGTATGYPOLIYA 179 MA AALLSYNLI ARKKOCDANNESY LOSINDATG YAYMTAALGWGTATGYPOLIYA 179 MA AALUSYLLI ARKKOCDANNESY LOSINDATG YAYMTAALGWGTATGYPOLIYA 179 MA AALUSYLLI AKKOCDANNESY LOSINDATG YAYMTAALGWGTATGYPOLIYA 179 MA AALUSYLLI AKKOCDANNESY LOSINDATG YAYMTAALGWGTATGYPOLIYA 179 MA AALUSYLLI AKKOCDANNESY LOSINDATG YAYMTAALGWGTATGYPOLIYA 179 MA AALUSYLLI AKKOCDANNESY LOSINDATG YAYMTAALGWGTAGYPOLIYA 179 MA TAY LISALU FAFROGDANISY LOSINDATG YAYMTAALGWGTAGYPOLIYA 179 MA TAY LISALU FAFROGDANISY LOSINDATG YAYMTAALGWGTAGYPOLIYA 179 MA TAY LIGYL YOFGOCONIKASY LOSINDATG YAYMYALLWGTAGYPONI 174 MA YU ISALU TURKENGCONINING LOSINDATG YAYMYALAWYGTUG TAYAD 174 MA YU YAYLLI TURKENGCANNESY LOSINDATG YAYMYALAWYGTUG TAYAD 174 MA YAYAL YAYNE YA TIYA LOSINDATG YAYMYALAYYOY TAYAT 179 LAYANYAYYYOYYOYYOYYOYYOYYOYYOYYOYYOYYONYA TAYAT 179 LAYANYALAYYYOYYOYYOYYOYYOYYOYYOYYOYYOYYOYYOYYOYY
M.maris_CDF3 M.maris_CDF2 H.baltiCa C.litoralis P.bernudensis Ruegeria sp. R.bacterlum C.P.marinum Silicibactor sp. C.salinarum Roseovarius sp. P.gilvum Acinetobacter sp. A.borkumensis C.psychroerythraea I.loihiensis N.oceani N.caesariensis H.influenzae H.somnus P.multocida P.stutzeri A.vinelandii Azoarcus sp.	LA LAR LASULT LRWREGDANVRSVGLSENDATG VGVUVAAGLAWTASPWEDLAVA 178 AAN LAQLTSVAIT LKWREGDANVRSVGLSENDATG VGVUAAGLAWTASPWEDLAVA 178 AAN LAQLTSVAIT LKWREGDSNVRSVGLSENDATG VGVUAAGLVSATGSANEDLFVG 177 LADAAALSFETULRWREGDSNVRSVGLSENDATG VGVUAAGLVSATGSANEDLFVG 177 LADAAALSFETULRWREGDANVRSVGLSENDATG VGVUAAGLVSATGSANEDLFVG 177 AAAALISVLI ARVKDCDANVRSVGLSENDATG VAVMTAALGVWGTATGWEDLVVA 178 MAAAALISVLI ARVKDCDANVRSVGLSENDATG VAVMTAALGVWGTATGWEDLVVA 179 MAAAALISVLI ARVKDCDANVRSVGLSENDATG VAVMTAALGVWGTATGWEDLVVA 179 MAAAALISVLI ARVKDCDANVRSVGLSENDATG VAVMTAALGVWGTATGWEDLVVA 179 MAAALUSVLI WRWRNGDANVRSVGLSENDATG VAVMTAALGVWGTATGWEDLVVA 179 MAAAQUSVLIJWRWRNGDANVRSVGLSENDATG VAVMTAALGVWGTATGWEDLVVA 179 MAAAQUSVLIJWRWRNGDANVRSVGLSENDATG VAVMTAALGVWGTATGWEDLVVA 179 LAMAAVSVLIJWRWRNGDANVRSVGLSENDATG VAVMTAALGVWGTGTSWDDLVVA 190 LAMAAVSVLIJWRWRNGDANVRSVGLSENDATG VAVMVAALAWGTETSWDDLVVA 180 LAMAAVSSVLIJWRWROCDANVRSVGLSENDATG VAVMVAALAWGTETSWDDLVVA 180 LAMAAVSSVLIJWRWROCDANVRSVGLSENDATG VAVMVAALAWGTETSWDDLVVA 180 LAMAAVSSVLIJWRWROCDANVRSVGLSENDATG VAVMVAALAWGTETSWDDLVVA 180 LAMAAVSSVLIJWRWROCDANVRSVGLSENDATG VAVMVAALAWGTETSWDDLVVA 180 LAMAAVSVSULJWRWROCDANVRSVGLSENDATG VAVMVAALAWGTETSWDLVVA 180 LAMAAVSVULJWRWROCDANVRSVGLSENDATG VAVMVAALAWGTETSWDLVVA 180 LAMAAVSVSVLJWRWROCDANVRSVGLSENDATG VAVMVAALSWRYGTSHSWDLVVA 180 LAMAAVSVSVLJWRWROCDANKSVGUS USENDATG VAVMVAALSWRYGTSHSWDLVVA 180 LAMAAVSVSVLJWRWROCDANKSVGUS USENDATG VAVVYFOSKVDLVVA 177 VAAANTVAVFOSKVGSVLSENDATG VAVVTAAAGVFGSGQAWELLVA 177 VAAAUVSVLJUTUKFROCDANNSVGUS VSSWGSENDATG VAVTIAAAGVFFGSGQAWELLVA 180 LAMAAVSVLJUTUKFROCDSNNSVGUS VSSWGSENDATG VAVTIAAAGVFFGSGSGNDLLVA 199 LAMAAVSVLJUTUKFROCDSNNSVGUS VSSWGSENDATG VAVTIAGAAVVFFGSKSCDLIVA 199 LAMAAMVASVLJUSCUSSUNGUS VSSWGSENDATG VAVTIAGAAVVFFGSKSCDLIVA 199 LAMAAMVAAVKSCLSSNDATG VAVTIAGAAVVFFGSKSCDLIVA 199 LAMAAMVAAVKSCLSSNDATG VAVTIAGAAVVFFGSKSCDLIVA 199 LAMAAMVAAVKEGSSMBSVGUS SENDATG VAVTIAGAAVVFFGSKSCDLIVA 199 LAMAAMVAAVKEGSSMBSVGUS USENDATG VAVTIAGAAVVFFGSKSCDLIVA 199 LAMAAGVALIM VAFRGCDANMRSVGUS SENDATG VAVTIAGAAVVFFGSKSCDLIVA 199 LAMAAG
M.maris_CDF3 M.maris_CDF2 H.baltica C.litoralis P.bernudensis Rueqeria sp. R.bacterium C.P.marinum Silicibacter sp. C.salinarum Roseovarius sp. P.gilvum Acinetobacter sp. A.borkumensis C.psychroerythraea I.loihiensis N.oceani N.oceani N.oceani N.caesariensis H.influenzae H.sonnus P.multocida P.stutzeri A.vinelandii A.varis_CDF3 M.maris_CDF3	LA TAR LASVLAT TURNERGOANNESV LUSENDATG VGVTVAAGLAWTASPREDLAVA 178 AAP LAQTESVAT TURNEGOSNNESV LUSENDATG VGVTAAGLAVATYNTAKEVELTVA 177 TAR LAQVASVETTURNEGOSNNESV LUSENDATG VGVTAAGELVSATGSANEDLEVA 177 TAA LAQUASVETTURNEGOSNNESV LUSENDATG VGVTAAGELVSATGSANEDLEVA 177 HAA LAQUSVETTURNEGOSNNESV LUSENDATG VGVTAAGELVSATGSANEDLEVA 178 MAAALISVULTARVEGOANNESV LUSENDATG VGVTAAGELVSATGSANEDLEVA 178 MAAALISVULTARVEGOANNESV LUSENDATG VAVITAAGVYETTOTAFOLTVA 179 MAAALISVULTARVEGOANNESV LUSENDATG VAVITAAGVYETTOTAFOLTVA 179 MAAALUSVLTARVEGOANNESV LUSENDATG VAVITAAGVYETTOTAFOLTVA 179 MAAALUSVLTARVEGOANNESV LUSENDATG VAVITAAGVYETTOTAFOLTVA 179 MAAVASVLTIRVEVGOANNESV LUSENDATG VAVITAAGVYETTOTAFOLTVA 179 MAAVASVLTIRVEVGOANNESV LUSENDATG VAVITAAGVYETOTAFOLTVA 179 MAAVASVLTIRVEVGOANNESV LUSENDATG VAVITAAGVYEGTASGOVDUVA 180 LASVISALTU FAFENGOANNESV LUSENDATG VAVITAAGVYEGTASGOVDUVA 180 LASVISALTU TERFOODANNESV LUSENDATG VAVITAAGVYEGTASGOVDUVA 170 MAAVASVLTIRVENGOANNESV LUSENDATG VAVITAAGVYEGTASGOVDUVA 174 LAAVANTACEFLI VERSONDANSV USENDATG VAVITAAGVYEGTASGOVDUVA 174 LAAVANTACEFLI VERSONDANSV USENDATG VAVITAAGVYEGSASVLTASNONTI 174 LAALVENGEFLI VERSONDENSV VUSENDATG VAVITAAGVYEFOSSETLINA 179 LAALVENGEFLI VERSONDENSV VUSENDATG VAVITAAGVYEFOSSETLINA 179 LAALVENGEFLI VERSONDENSV VUSENDATG VAVITAGAVYEFOSSETLINA 179 LAALVENGENSNESV VUSENDATG VAVITAGAAVYEFOSSETLINA 179 LAALVAAVALTIKEFDOEDSNESV VUSENDATG VAVITAGAAVYEFOSSETLINA 179 LAALAVAAVALTIKEFDOEDSNESV VUSENDATG VAVITAGAAVYEFOSSETLINA 179 LAALAVAAVALTIKEFDOEDSNESV VUSENDATG VAVITAGAAVYEFOSSETLINA 179 LAALAVAAVALTIKEFDOEDSNESV VUSENDATG VAVITAGAAVYEFOSSETLINA 179 LAALAVAAMINAAFECEDSNESV VUSENDATG VAVITAGAAVYEFOSSETLINA 179 LAALAVAAMINAAFECEDSNESV VUSENDATG VAVITAGAAVYEFOSSETLINA 179 LAALAVAAMINAAFECEDANNESV LUSENDATG VAVITAGAAVYEFOSSEVENTIVA 179 LAAVAAGVALMINAF
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M.maris_CDF3 M.maris_CDF2 H.baltiCa C.litoralis P.bermudensis Ruegeria sp. R.bacterium C.P.marinum Sillcibacter sp. C.salinarum Roseovarius sp. P.gilvum Acinetobacter sp. A.borkumensis C.paychroerythraea I.loihiensis N.oceani N.	LA LAR LASULAT LEWREGDANVRSVGLSENDATG VGVTVAAGLAWTASPWEDLAVA 178 AAPLAALTSVAIT LEWREGDANVRSVLSENDATG VGVTVAAGLAWTASPWEDLAVA 178 AAPLAALTSVAIT LEWREGDSNVRSVLSENDATG VGVTVAAGLAVATYNTAKE VGVTVAAGLAVATYNTAKE HAL VGSVETTUERNEGDSNVRSVLSENDATG VGVTVAAGLAVATYNTAKE HAL LSVALL LEWREGDANVRSVLSENDATG VGVTVAAGLAVATTGVEDLEVG 177 LA AALLSVALL ARKKDCDANVRSVLSENDATG VGVTVAAGLAVATTGVEDLEVG 178 MAAALLSVALLARKKDCDANVRSVLSENDATG VAVMTAALGVWGTATGVEDLEVA 179 MA AALLSVALLARKKDCDANVRSVLSENDATG VAVMTAALGVWGTATGVEDLEVA 179 MA AALLSVALLARKKDCDANVRSVLSENDATG VAVMTAALGVWGTATGVEDLEVA 179 MA AALLSVALLARKKDCDANVRSVLSENDATG VAVMTAALGVWGTATGVEDLEVA 178 LATAALLSVALLARKKDCDANVRSVLSENDATG VAVMTAALGVWGTATGVEDLEVA 178 LATAALLSVALLMAKKDCDANVRSVLSENDATG VAVMTAALGVWGTATGVEDLEVA 178 LATAALLSVALLMAKKDCDANVRSVLSENDATG VAVMTAALGVWGTASGVEDLEVA 178 LATAALLSVALLMAKKDCDANVRSVLSENDATG VAVMTAALGVWGTASGVEDLEVA 178 LATAALGSVLLMWRKDCDANVRSVLSENDATG VAVMTAALGVWGTASGVEDLEVA 170 MG TAAVSSLLUMRYKDCDANVRSVLSENDATG VAVMTAALGVWGTASGVEDLEVA 180 LATAALGVSLLUMRYKDCDANVRSVLSENDATG VAVMTAALGVWGTASGVEDLEVA 180 LATAALGVSLLUMRYKDCDANVRSVLSENDATG VAVMTAALGVWGTASGVEDLEVA 180 LATAALGVSLLUMRYKDCDANVRSVLSENDATG VAVMTAALGVWGTASGVEDLEVA 180 LATAALGVSLLUMRYKDCDANVRSVLSENDATG VAVMTAALGVWGTASGVEDLEVA 180 LATAALGVSLLUMRYKDCDANVRSVLSENDATG VAVMTAALGVWGTASGVEDLEVA 180 LATAALGVSLLUMRYKDCDANVRSVLSENDATG VAVMTAALGVWGTASGVEDLEVA 180 LATAALGVSLLUMRYKDCDSNVRSVVSENDATG VAVTLAGAVYFFOSKYDLEVA 180 LATAALGVSLLUMRYKDCDSNVRSVVSENDATG VAVTLAGAVYFFOSKYDLEVA 180 FVLAGF LYRKERCOSNNRSVVSENDATG VAVTLAGAVYFFOSKYDLEVA 179 LATAALTVALLUKERDCOSNVRSVVSENDATG VAVTLAGAVYFFOSKYDLEVA 179 LATAALGVALMYAFREGDSNNRSVVSENDATG VAVTLAGAVYFFOSKYDLEVA 179 LATAALGVALMYAFREGDSNNRSVVSENDATG VAVTLAGAVYFFOSKYDLEVA 179 LATAALGVALMYAFREGDSNNRSVVSENDATG VAVTLAGAVYFFOSKYDLEVA 179 LATAALGVALMYAFREGDSNNRSVVSENDATG VAVTLAGAVYFFOSKYDLEVA 179 LATAALGVALMYAFREGDSNNRSVVSENDATG VAVTLAGAVYFFOSKYDLEVA 179 LATAALGVALMYAFREGDSNNRSVVSENDATG VAVTLAGAVYFFOSKYDLEVA 179 LATAALGVALMYAFREGDSNNRSVVSENDATG VAVTLAGAVYFFOSKYDLEVA 179 LATAALGVALMYAFREGDSNNRSVVSEND
M.maris_CDF3 M.maris_CDF3 H.baltLca C.litoralis P.bermudensis Ruegeria sp. R.bacterium C.P.marinum Silicibacter sp. C.salinarum Roseovarlus sp. P.gilvum Acinetobacter sp. A.borkumensis C.psychroerythraea I.loihiensis N.cceanis M.cceanis H.influenzae H.somnus P.multocida P.sutzeri A.vinelandii Azvarcus sp. M.maris_CDF3 M.maris_CDF3 M.maris_CDF3 M.maris_CDF3 M.maris_CDF3 M.maris_RCF3 F.bermudensis Ruegeria sp.	LA LAGLASVLIT LRWREGDANVRSVGLSENDATG VGVTVAAGLVAWTASPW POLAVA 177 AAA LAGLYSVAIT LWRDGDSNVSVGLSENDATG VAVILASAAVAYNTNKAPELIVA 177 IAA LAGVASVFTJLRWREGDSNVSVGLSENDATG VGVTAAGFLVSATGSAMEDLFVG 177 LAAAALASTELJRWREGDSNVSVGLSENDATG VGVTAAGFLVSATGSAMEDLFVG 177 HAAAALSTELJRWREGDANVRSVGLSENDATG VGVTAAGFLVSATGSAMEDLFVG 178 MAAAALISVLI ARVKDCDANVRSVGLSENDATG VAVMTAALGVWGTATGWPLLVA 178 MAAAALISVLI ARVKDCDANVRSVGLSENDATG VAVMTAALGVWGTATGWPLLVA 178 MAAAALISVLI ARVKDCDANVRSVGLSENDATG VAVMTAALGVWGTATGWPLLVA 179 MAAAALUSVLI MRVKDCDANVRSVGLSENDATG VAVMTAALGVWGTATGWPLLVA 179 MAAAALUSVLI MRVKDCDANVRSVGLSENDATG VAVMTAALGVWGTATGWPLLVA 179 MAAAALUSVLI MRVKDCDANVRSVGLSENDATG VAVMTAALGVWGTATGWPLLVA 179 LAMAAVASVLILMRWRDCDANVRSVGLSENDATG VAVMTAALGVWGTATGWPLLVA 179 LAMAAVASVLILMRWRDCDANVRSVGLSENDATG VAVMTAALAVWGTETGWPLLVA 178 LAVAAVSVSULLMRWRDCDANVRSVGLSENDATG VAVMTAALAVWGTETGWPLLVA 179 LAMAAVASVLILMRWRDCDANVRSVGLSENDATG VAVMTAALAVWGTETGWPLLVA 170 MG LAQVISALULMRWRDCDANVRSVGLSENDATG VAVMTAALAVWGTETGWPLLVA 170 LAMAAVASVLILMRWRDCDANVRSVGLSENDATG VAVMTAALAVWGTETGWPLLVA 170 LAMAAVASVLILMRWRDCDANVRSVGLSENDATG VAVMTAALAVWGTETGWPLLVA 180 LAMAAVASVLILMRWRDCDANVRSVGLSENDATG VAVMTAALAVWGTETGWPLLVA 180 LAMAAVASVLILMRWRDCDANVRSVGLSENDATG VAVMTAALSWWGTETGWPLLVA 180 LAMAVVSVGCGDANKSVGUSENDATG VAVMTAALSWWGTETGWPLLVA 180 LAMAVVSVGCGDANKSVGVSENDATG VAVMTAALSWYFFGSLSVELLVA 174 177 VAAAAVVSVLILLTERFEGDANKSVGVSENDATG VAVTLAAAVVFFGSLSVELLVA 179 LAMAVVSVLILLUKFEDDSNVRSVGVSENDATG VAVILLAAASVYFFGSLSVELLVA 179 LAMAVVSVLILTUKFEDDSNVRSVGVSENDATG VAVILLAAASVFFGSLSVELLVA 179 LAMAVASVLILTUKFEDDSNVRSVGVSENDATG VAVILLAAAVVFFGSLSVELLVA 179 LAMAVASVLITUKFEDCDSNVRSVGVSENDATG VAVILLAAAGVFEGSGAWPETUVA 179 LAMAVASVLITUKFEDCDSNVRSVGVSENDATG VAVILLAAAGVFEGTGSGEVELLVA 179 LAMAAGVALMI VAFREDCDANMRSVGLSENDATG VAVILLAAAGVFEGTGSCEVELVA 179 LAMAAGVALMI VAFREDCDANMRSVGUSENDATG VAVILLAAAGVFEGTGSCEVELVA 179 LAMAAGVALMI VAFREDCDANMRSVGLSENDATG VAVILLAAGVFEGTGSCEVELVA 178 LAMAAGVALMI VAFREDCDANMRSVGLSENDATG VAVILLAAGVFEGTGSCEVELVA 178 LAMAAGVALMI VAFREDCDANMRSVGLSENDATG VAVILLAAGVFEGTGS
M.maris_CDF3 M.maris_CDF2 H.baltLGa C.litoralis P.bermudensis Ruegeria sp. R.bacterium C.P.marinum Sillcibactor sp. C.salinarum Roseovarius sp. P.gilvum Acinetobacter sp. A.borkumensis C.psychroerythraea I.loihiensis N.oceani N.oceani N.oceani N.oceani N.oceani M.maris_CDF3 M.m	LA LAGLASVLIT LRWREGDANVRSVGLSENDATG VGVTVAAGLAWTASPWEDLAVA 178 AAPLAALTSVAIT LKWREGDANVRSVLSENDATG VGVTVAAGLAWTASPWEDLAVA 178 AAPLAALTSVAIT LKWREGDANVRSVLSENDATG VGVTVAAGLAVATYNTAKEVELTVA 177 LA AALLASVLJLWREGDANVRSVLSENDATG VGVTVAAGLAVATYNTAKEVELTVA 177 LA AALLSVLLUWREKDGANVRSVLSENDATG VGVTVAAGLAVKLTGSANEDLEVG 177 LA AALLSVLLUWREKDGANVRSVLSENDATG VGVTVAAGLAVKLTGSANEDLEVG 178 MAAALLSVLLUWREKDGANVRSVLSENDATG VAVMTAALGVWGTATGWEDLEVA 178 MAAALLSVLLUWREKDGANVRSVLSENDATG VAVMTAALGVWGTATGWEDLEVA 178 MAAALLSVLLUWREKDGANVRSVLSENDATG VAVMTAALGVWGTATGWEDLEVA 179 MA AALLSVLLUWREKDGANVRSVLSENDATG VAVMTAALGVWGTATGWEDLEVA 178 LATTAALLSVLLUWREKDGANVRSVLSENDATG VAVMTAALGVWGTATGWEDLEVA 178 LATTAALLSVLLUWREKDGANVRSVLSENDATG VAVMTAALGVWGTATGWEDLEVA 178 LATAALLSVLLUWREKGDANVRSVLSENDATG VAVMTAALGVWGTASGNEDLEVA 178 LATAALLSVLLUWREKGDANVRSVLSENDATG VAVMTAALGVWGTASGNEDLEVA 178 LATAALLSVLLUWREKGDANVRSVLSENDATG VAVMTAALGVWGTASGNEDLEVA 178 LATAALGSVLLMWREKGDANVRSVLSENDATG VAVMTAALGVWGTASGNEDLEVA 178 LATAALVSSVLLUWREKGDANVRSVLSENDATG VAVMTAALGVWGTASGNEDLEVA 179 MG TAAVTSALLTEREKGGOANNESVLSENDATG VAVMTAALGVWGTASGNEDLEVA 170 MA AALGVSLLUWREKGGOANNESVLSENDATG VAVMTAALGVWGTASGNEDLEVA 170 LATAALGVSLLUWREKGGOANNESVLSENDATG VAVMTAALGVWGTASGNEDLEVA 180 LATSAVTSALLTUREKGGOANNESVLSENDATG VAVMTAALGVWGTASGNEDLEVA 180 LATSAVTSALLTUREKGGOANNESVLSENDATG VAVMTAALGVWGTASGNEDLEVA 180 LATAALVSVLSENDLEVSLSENDATG VAVMTAAGVEFGSGANELEVA 180 LATAVTSALLTURERDGOSNVRSVVSENDATG VAVTLAGAVYFFQSKYDLEVA 179 LATAVTATGVEFT VANTERDOGSNVRSVVSENDATG VAVTLAGAVYFFQSKYDLEVA 179 LATAVTAAMTYATEGGOSNNESVVSENDATG VAVTLAGAVYFFQSKYDLEVA 179 LATAVAAMTYATEGGOSNNESVVSENDATG VAVTLAGAVYFFQSKYDLEVA 179 LATAVAAMTYATEGGOSNNESVVSENDATG VAVTLAGAVYFFQSKYDLEVA 179 LATAVAAMTYATEGGOSNNESVVSENDATG VAVTLAGAVYFFQSKYDLEVA 178 LATAVAAMTYATEGGOSNNESVVSENDATG VAVTLAGAVYFFQSKYDLEVA 179 LATAGVALMTYAFFEGDANNESVUSENDATG VAVTLAGAVFFGGGGVEFTLVA 178 LATAVAAMTYATEGGOSNNESVVSENDATG VAVTLAGAVFFGGGGVEFTLVA 178 LATAVAAMTYAFFEGDANNESVUSENDATG VAVTLAGAVFFGGGGVEFTLVA 179 LATAVAAMTYATEGGOSNNESVVSENDATG VAVTLAGAVFFGGGSK
M.maris_CDF3 M.maris_CDF2 H.baltiCa C.litoralis P.bernudensis Ruegeria sp. R.bacterlum C.P.marinum Silicibactor sp. C.salinarum Roseovarius sp. P.gilvum Acinetobacter sp. A.borkumensis C.psychroerythraea I.loihiensis M.oceani M.caesariensis H.influenzae H.somnus P.multocida P.stutzeri A.vinelandii Azoarcus sp. M.maris_CDF3 M.maris_CDF3 M.maris_CDF3 M.maris_CDF3 R.bacterium C.P.mathana	LA LAGLASVLIT LRWREGDANVRSVGLÜSENDATG VGVTVAAGLVAWTASPWEDLAVA 178 AAN LAGLTSVAIT LWREGDGSNVRSVGLÜSENDATG VGVTAAGSTVAYTNTANEPULTVA 177 AAN LAGLTSVAIT LWREGDGSNVRSVGLÜSENDATG VGVTAAGSTVAYTNTANEPULTVA 177 LADAAGLASTELLURWREGDGSNVRSVGLÜSENDATG VGVTAAGSTVATGSAMEDLEVG 177 LADAAGLASTELLURWREGDANVRSVGLÜSENDATG VGVTAAGSTVATGSAMEDLEVG 177 AAN AAGLTSVLILARVKDCDANVRSVGLÜSENDATG VGVAMTAALGVWGTATGWEDLUVA 178 MAAAGLTSVLILARVKDCDANVRSVGLÜSENDATG VGVAMTAALGVWGTATGWEDLUVA 179 MAAAGLTSVLILARVKDCDANVRSVGLÜSENDATG VAVMTAALGVWGTATGWEDLUVA 179 MAAAGLTSVLILMRVKDCDANVRSVGLÜSENDATG VAVMTAALGVWGTATGWEDLUVA 179 MAAAGLUSVLILMRVKDCDANVRSVGLÜSENDATG VAVMTAALGVWGTATGWEDLUVA 179 LAMAAQVASVLILMRVKDCDANVRSVGLÜSENDATG VAVMTAALGVWGTATGWEDLUVA 179 LAMAAQVASVLILMRVKDCDANVRSVGLÜSENDATG VAVMTAALGVWGTATGWEDLUVA 179 LAMAAQVASVLILMRVKDCDANVRSVGLÜSENDATG VAVMTAALGVWGTGTSWEDLUVA 179 LAMAAQVASVLILMRVKDCDANVRSVGLÜSENDATG VAVMTAALGVWGTGTSWEDLUVA 180 LANAAVSSULIMRVKDCDANVRSVGLÜSENDATG VAVMVAALGVWGTGTSWEDLUVA 180 LANAAVSSULIMRVKDCDANVRSVGLÜSENDATG VAVMVAALGVWGTGTSWEDLUVA 180 LANAAVSULILRRFKDCDANNKSVGLÜSENDATG VAVMVAALGVWGTGTSWEDLUVA 180 LANAAVSULILKERDCDANNKSVGLÜSENDATG VAVMVAALGVWGTGTSWEDLUVA 180 LANAAVSULILKERDCDANNKSVGLÜSENDATG VAVMVAALGVWGTGSGNEDLUVA 180 LANAAVSULILKERDCDANNKSVVGLÜSENDATG VAVMVAALGVWGTGSGNEDLUVA 180 LANAAVVSULILKERDCDANNKSVVGLÜSENDATG VAVMVAALGVWGTGSGONEDLUVA 180 LANAAVVSULILKERDCDANKSVVGUSENDATG VAVUTAAGAVEFGSGONEDLUVA 180 LANAAVVSULITUKERDCDANKSVVGUSENDATG VAVUTAAAGVYEFGSKYDELUVA 199 LANAAVVYFFOSKYDUVSVVGENDATG VAVUTAAAGVYEFGSKYDELUVA 199 LANAAVVYFFOSKYDUVSVVGENDATG VAVUTAAAGVYEFGSKYDELUVA 199 LANAAVVFFOSKSVUVSENDATG VAVUTAAAGVEFGGSKEDLUVA 199 LANAAVVFFOSKSVUVSVVGENDATG VAVUTAAAGVEFGGSKEDLUVA 199 LANAAVVFFOSKSVUVSENDATG VAVUTAAAGVEFGGSKEDLUVA 199 LANAAVVFFOSKSVUVSENDATG VAVUTAAAGVEFGGSKEDLUVA 199 LANAAVVFFOSKSVUVSENDATG VAVUTAAAGVEFGGSKEDLUVA 199 LANAAVVFFOSKSVUVSENDATG VAVUTAAAGVEFGGSKEDLUVA 199 LANAAVVFFOSKSVUVSENDATG VAVUTAAAGVEFGGSKEDLUVA 199 LANAAVVFFOSKSUVSVVSENDATG VAVUTAAAGVEFGGSKEDLUVA 199 LANAAVVFFOSKSVUVSENDATG VAVUTAAAGVEFGGSK
M.maris_CDF3 M.maris_CDF2 H.baltica C.litoralis P.bermudensis Ruegeria sp. R.bacterium C.P.marinum Silicibacter sp. C.salinarum Roseovarius sp. P.gilvum Acinetobacter sp. A.borkumensis C.psychroerythraea I.loihiensis N.coeani N.caesariensis H.influenzae H.somus P.multocida P.stutzeri A.vinelandii A.vorelas sp. M.maris_CDF3 M.maris_CDF3 H.baltica C.litoralis P.bacterium C.P.marinum Silicibater sp.	LA TAR LASVLAT TURNERCOANVESVELSENDATC VGVTVAACLAWTASPKPELAVA 178 AAPLAAUTSVAIT TURNERCOSNVESVELSENDATC VGVTVAACTAWTNASPKPELIVA 177 IA LA VASVETU FURNEOGSNVESVELSENDATC VGVTVAACTAVENTNAVETUVA 177 LA AALASIFTU FURNEOGSNVESVELSENDATC VGVTVAACTAVENTNAVETUVA 177 LA AALASIFTU FURNEOGSNVESVELSENDATC VGVTVAACTAVENTNAVETUVA 178 LAALASIFTU FURNEOGSNVESVELSENDATC VGVTVAACTAVENTNAVETUVA 178 LAALASIFTU FURNEOGSNVESVELSENDATC VGVTVAACTAVENTVATUVATUVA 178 LAALASIFTU FURNEOGSNVESVELSENDATC VGVTVAACTAVENTUVA 178 LAALSISVEL FURNEOGSNVESVELSENDATC VAVITAAGUVETTGTAVED LUVA 178 LAATAALISVEL FARKOGDANVESVELSENDATC VAVITAAGUVETTGTAVED LUVA 179 LAATAALISVEL KAVKOGDANVESVELSENDATC VAVITAAGUVETTGTAVED LUVA 179 LAATAALUSVLI KAVKOGDANVESVELSENDATC VAVITAAGUVETGTASVED LUVA 180 LAASAVITSALLI KAKOGDANVESVELSENDATA VAVITAAGUVETGTASVED LUVA 180 LAASAVITSALLI LIKROGDANINSVELSENDATA LISKITATIS GETLIVVELDSRNPELIVA 176 LAAVISVELIVENESSENDINKSVELSENDATAGUVETGTAALVEVENTG 174 LAAVITSALLI LIKROGDANINSVELSENDATAGUVETTIS GETLIVVELDGENVENDUTG 174 LAAVITSALLI LIKROGDANINSVELSENDATAGUVETTIS GETLIVVELDGENVENDUTG 174 LAAVITSALLI LIKROGDANINSVELSENDATAGUVETTIS GETLIVVELDGENVENDUTG 174 LAAVITSALLI LIKROGDANINSVELSENDATGUVETTIS GETLIVVELDGENVENDUTG 174 LAAVITAALVYTENEODSNNESVENDENSMENTIS USENDATAGUVETGSGAVETLIVA 179 LAALVAAMIYAYKEGDSNNESVENDENSMENTIS USENDATGUVAVITGASVETGISGUVELIVA 179 LAALVAAMIYAKEGDSNNESVELSENDATGUVAVITGASVETGISGUVELIVA 179 LAAVAMIYAKEGDSNNESVELSENDATGUVETNATTGUVETGISGUVELIVA 179 LAALVAAMIYAKEGDSNNESVELSENDATGUVETNATTGUVETGISGUVELIVA 179 LAAVAMIYAKEGDSNNESVELSENDATGUVETNATTGUVETGISGUVELIVA 179 LAAVAMIYAKEGDSNNESVELSENDATGUVETNATTGUVETGISGUVELIVA 179 LAAVAAMIYAKEGDSNNESVELSENDATGUVETNATTGUVETGUSEVELIVA 179 LAAVAAMIYAKEGDSNN
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Fig. 5. Sequence analysis of chosen CTD-lacking CDFs. The sequence alignment was prepared using ClustalW [55,28]. The identical residues are highlighted in dark green; the highly similar and similar residues are highlighted in bright and pale green, respectively. The residues comprising the active site are highlighted in red. Potential zinc coordinating residues are highlighted in blue. The following sequences have been used for the alignment: YP_757562 and YP_755370 (Maricaulis marisMCS10), YP_003059113 (Hirschiabaltica ATCC 49814), ZP_01104777 (Congregibacter litoralis KT71), YP_003855988 (Parvularcula bermudensis HTCC2503), ZP_05087944 (Ruegeria sp. R11); ZP_05078287 (Rhodobacterales bacterium Y4I), YP_003551326 (Candidatus Puniceispirillummarinum IMCC1322), ZP_05742081 (Silicibacter sp. TrichCH4B), ZP_18917629 (Caenispirillum salinarum AK4), ZP_01878497 (Roseovarius sp. TM1035), YP_004305950 (Polymorphum gilvum SL003B-26A1), YP_048060 (Acinetobacter sp. ADP1), YP_691965 (Alcanivorax borkumensis SK2), YP_268686 (Colwellia psychrerythraea), YP_155164 (Idiomarina loihiensis L2TR), YP_343548 (Nitrosococcus oceani ATCC19707), WP_007022919 (Neptuniibacter caesariensis), ZP_01786903 (Haemophilus influenzae R3021), YP_001785060 (Haemophilus somnus 2336), NP_246881 (Pasteurella multocida Pm70), YP_007240895 (Pseudomonas stutzeri RCH2), YP_002799611 (Azotobacter vinelandii), YP_934444 (Azoarcus sp. strain BH72).

Table	1
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Examples of occurrence of CTD-lacking CDFs.

Organism	CTD-lacking CDF(s) locus/length (aa)	Classical CDF(s) locus/length (aa)
Maricaulis maris ^a	MmCDF3 YP_757562/ 211 MmCDF2 YP_755370/ 228	YP_755350/323
Parvularcula bermudensis HTCC2503 ^a	YP_003855988/229 YP_003855674/199 YP_003855983/213	YP_003855791/303 YP_003855987/308 YP_003855997/296 YP_003854925/339
Limnobacter sp. MED105 ^a	WP_008249295/218 WP_008246900/220	WP_008249248/ 307
Silicibacter sp. TrichCH4B ^a Hirschia baltica ATCC 49814 ^a	ZP_05742081/220 YP_003059113/214	ZP_05741491/304 YP_003060806/320 YP_003059495/328
Nitrosococcus oceani ^a	YP_343548/225	YP_344847/317 YP_343784/321 YP_342644/298
Alcanivorax borkumensis SK2 ^a	YP_691965/207	YP_692892/304 YP_693094/307 YP_694190/318 YP_694197/314
Idiomarina loihiensis L2TRª	YP_155164/211	YP_155022/298 YP_155631/298 YP_156018/258 YP_156023/295 YP_156812/309 YP_156968/292
Candidatus Puniceispirillum marinum IMCC1322ª	YP_003551326/211	
Haemophilus influenzae R3021 ^b	ZP_01786903/204	
Haemophilus somnus 2336 ^b Pasteurella multocida Pm70 ^b Pseudomonas stutzeri RCH2 ^b	YP_001785060/204 NP_246881/204 YP_007240895/215	YP_001785107/298 NP_245005/304 YP_007238809/296 YP_007238849/306 YP_007241297/320
Polymorphum gilvum SL003B- 26A1 ^c	YP_004305950/218	YP_004301979/295
Acinetobacter sp. ADP1 ^c	YP_048060/214	YP_047861/307 YP_045208/325
Bradyrhizobium japonicum USDA 6 ^d	YP_005609608/238	YP_005609603/271
Agrobacterium albertimagni AOL15 ^d	ZP_11176199/237	ZP_11175205/302 ZP_11174117/300
Azotobacter vinelandii	YP_002799611/212	YP_002798204/293

^a Marine bacteria.

^b Pathogenic bacteria.

^c Soil bacteria.

^d Nitrogen cycle bacteria.

do exist as independent proteins, it would be reasonable to suggest that they work in tandem with CTD-lacking CDFs to achieve divalent metal cation transport. Many CDFs may also be part of metal tolerance gene clusters such as those found in the pA81 plasmid which plays a role in Zn^{2+} , Pb²⁺ and Cd²⁺ tolerance in *A. thaliana*. This cluster of genes also includes a putative P1-ATPase [39]. In addition, based on the recent findings about the various CDF members, it is also plausible to hypothesize that they could, perhaps in certain conditions, mediate ion import.

For obvious reasons, the CTD-lacking CDFs cannot function according to the scissoring mechanism that assumes that the CTD is a crucial player in Zn^{2+} sensing, binding and initiating conformational changes within the TMDs believed to be necessary for zinc transport. This model can neither be applied for ZitB from *E. coli* or CzcD from *C. metallidurans* as the corresponding CTDs, although important for the full function of the protein, were shown not to be essential for ion transport [2]. The alternating access mechanism of action does not envisage direct involvement of CTDs in ion transport and instead, the CTD is pictured as a necessary element for protein stability. The recent discovery of the

CTD-lacking CDFs clearly shows that these proteins are functional and stable without involvement of their cytoplasmic domains. With the potential for protein dimerization mediated by other area(s), *e.g.* their N-terminus or, in some cases, their C-terminus, we postulate that they may also be involved in the formation of the additional ion binding site, it is plausible that CTD-lacking CDFs may function according to the alternating mechanism of action.

10. Concluding remarks

To date, only one high resolution structure of a full length CDF, YiiP from E. coli, is available. Recent reports, including the identification of the CTD-lacking CDF subfamily, provide an extreme diversity in this family of proteins that simply cannot be defined based on the structural elucidation of a single member. The new findings in the field of CDFs raise more and more questions, rather than answering the existing ones. What is the exact role of the CTD? How are the metal ions supplied to the transporters? What is the role of metal binding site B? How is the ion specificity achieved? Do all the members of the family act according to the same mechanism of action and which one is it? Those and many more unanswered questions accumulated during recent years call for intensified efforts in characterization and ultimately crystal structure determination of various members of the family. What is beginning to become clearer from CDF studies is that CDFs can exist as fully functional divalent metal cation transporters in both classical and truncated forms which lack a pronounced cytoplasmic domain. We also have evidence which suggests that certain CDFs have the capability of transporting or at least binding several differing divalent metal cations and this cation selectivity is dependent on several differing functional motifs. It is also apparent that CDFs can be transporters of a sole cation or, in many cases, transport more than one divalent cation. Intensified characterization will require the overexpression and purification of these membrane proteins and subsequent in vivo functional analysis which is further validated by more precise characterization measurements performed on purified CDFs. Biophysical characterization using techniques such as ITC, SEC-MALS, proteoliposome-based transport assays and surface plasmon resonance will shed light on metal binding, the oligomeric state of the transporter, the transport kinetics and protein-protein or protein-membrane interactions, respectively. Routine structural analysis of these proteins, however, proves complex and time consuming. In order to elucidate the YiiP structure, more than 3000 crystals have been screened as only a small fraction of the obtained crystals were of data collection quality. Moreover, 31 out of 102 collected datasets had to be merged for structure determination at 3.8 Å while 25 crystals were used to generate a merged dataset of 2.9 Å due to severe radiation damage of the crystals [62,63]. This difficulty in crystallization and data collection means that it is highly likely that all available techniques and methods will have to be exhausted to obtain large amounts of structural data for the family. Some options which could be explored include in-meso and bicelle crystallization methods which may help facilitate the generation of structure-grade crystals. The cubic phase technique in particular seems promising as it has been successfully utilized for the crystallization of a number of challenging membrane proteins and membrane protein complexes such as several G-protein coupled receptors (e.g. [84,67,36,34,110] and caa₃-cytochrome c oxidase [64], respectively. Only such thorough and comprehensive approaches, combined with detailed functional analysis of various CDF members will allow us to understand the mechanisms within this interesting and diverse family of proteins that for now remain elusive.

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