



# Key Knowledge Gaps to Fill at the Cell-To-Ecosystem Level in Marine B-Vitamin Cycling

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B-vitamins are essential micronutrients for marine plankton. Additionally, we now know many marine plankton cannot synthesize B-vitamins *de novo* (from scratch) and thus are reliant on external supplies. Details of B-vitamin exchange, whether ‘active’ or ‘passive’ (i.e. through cell secretion or mortality), are lacking and as a result we struggle to predict microbial physiology, community composition and biogeochemistry. We argue that significant advances in understanding of the impact of B-vitamin exchange and cycling on marine community structure and biogeochemistry can be made by focusing on unknowns related to the ‘in’s and out’s’ of B-vitamin transport, exchange between plankton, and ecosystem scale processing/transformation of B-vitamins. We point out that it is particularly necessary to reach beyond traditional categorization of populations as B-vitamin auxotrophs (requiring supplied vitamin) or prototrophs (*de novo* vitamin synthesizers) and begin addressing which populations are net ‘providers’ and/or ‘consumers’. This is a particularly interesting problem as organisms cannot be confidently categorized as net ‘providers’ and/or ‘consumers’ based on genome-based prediction, and it is possible the two roles may change over time and environmental conditions. We posit that greater knowledge of B-vitamin exchange, e.g. cross-feeding, acquisition and secretion systems, environmental triggers of ‘provision’ and ‘consumption’, will reveal unforeseen networking and novel niches across marine planktonic communities. Last, we advocate for further experiments tracking the responses of isolates or natural communities relative to vitamin availability, tracing flow of B-vitamins between cells using novel approaches (e.g. isotopic, fluorometric), and greater consideration of altered B-vitamin exchange and cycling under future climate scenarios.

**Keywords:** nutrient cycling, marine plankton, B-vitamin, vitamin B12, vitamin B1, microbial interactions, cross-feeding, auxotrophy

## INTRODUCTION

Exchange, cycling, and availability of B-vitamins in the ocean are poorly understood despite their necessity for marine life. In brief, B-vitamins are required in minute amounts (e.g. 10-1000's of molecules) by cells and function as enzyme cofactors, riboswitch ligands, and/or antioxidants (Lukienko et al., 2000; Miranda-Rios et al., 2001; Frank et al., 2007). Early cultivation experiments revealed B-vitamin auxotrophic (those unable to synthesize a vitamin *de novo*) and prototrophic (cells capable of *de novo* B-vitamin synthesis) marine plankton (Provasoli and Pintner, 1953; Burkholder, 1963; Provasoli and Carlucci, 1974). The development of molecular methods and continued cultivation efforts have revealed more about the steps in B-vitamin biosynthesis, salvage of vitamins from simpler fragments, and potential sources and sinks [see reviews by (Croft et al., 2006; Jurgenson et al., 2009; Gray and Escalante-Semerena, 2010; Butzin et al., 2013; Sañudo-Wilhelmy et al., 2014; Helliwell, 2017)]. After a half-century lull, interest in B-vitamins has revitalized largely following the recognition that prevalent and/or biochemically influential marine plankton are auxotrophic for one or more B-vitamins (Tang et al., 2010; Carini et al., 2014; Gutowska et al., 2017; Helliwell, 2017; Gómez-Consarnau et al., 2018; Paerl et al., 2018b) and the development of chemical methods to measure B-vitamins from seawater (Sañudo-Wilhelmy, 2012; Heal, 2014; Suffridge et al., 2017). Several new unknowns emerge from these recent findings and working to address them is expected to increase our ability to predict plankton composition, productivity, and plankton-driven cycling of elements (e.g. C, N, S) with climate and biological impact. Specifically, there are key knowledge gaps in the areas of: 1) cellular acquisition and provision; 2) microbe-microbe interactions; and 3) marine communities and ecosystem(s) that merit immediate attention. Soil and gut-microbiome related B-vitamin research (e.g. microbial vitamin salvage or vitamin remodeling) is ahead of oceanographic research and can provide perspectives on B-vitamin exchange and cycling potentially occurring in the ocean (Jenkins et al., 2007; Yi et al., 2012; Costliow and Degnan, 2017; Sharma et al., 2019; Sokolovskaya et al., 2020). We see B-vitamin exchange and cycling in the sea as ripe for exploration and offer several perspectives for filling near-term and future needs in this research area.

### 1. Investigating the “In’s and Out’s” of Transport at the Cellular Level

Most marine plankton are auxotrophic for one or more B-vitamins (Gómez-Consarnau et al., 2018; Paerl et al., 2018b) and thus rely on exogenous B-vitamins or vitamers (related compounds, e.g. precursors derived from *de novo* biosynthesis or degradation) to survive. Notably, some prototrophic plankton and those not requiring certain B-vitamins can also use exogenous B-vitamins/vitamins in seawater (Droop, 1968; Agarwal et al., 2019). These users of exogenous B-vitamins/vitamins are considered ‘consumers’ in the ocean. Accordingly, uptake transporters (importers) that enable B-vitamin/vitamer

acquisition, and exporters that flux B-vitamin/vitamer to the public pool in seawater, influence B-vitamin/vitamer availability for diverse auxotrophic and prototrophic plankton that mediate elemental/energetic cycling and food web structure in the ocean.

Several importers are known based on experimentation with non-marine model microbes or are proposed based on proximity of transporter coding genes to B-vitamin biosynthesis genes or riboswitches in prokaryotes and eukaryotes (Gutiérrez-Preciado et al., 2015; Rodionova et al., 2015; Anderson et al., 2016; Rodionov et al., 2019). Nonetheless, key knowledge gaps remain. For example, most importer functionality is predicted based on comparative genomics (Carini et al., 2014; McRose et al., 2014; Gómez-Consarnau et al., 2018; Paerl et al., 2018b), leaving a current need for more direct experiments that clarify functionality (e.g. substrate binding affinity, uptake kinetics) of importers (Gray and Escalante-Semerena, 2010; Rodionova et al., 2015; Anderson et al., 2016; Rosnow et al., 2018). This is especially the case given that some importers may aid the uptake of vitamers or other nutrients, e.g. TonB-dependent transport systems facilitate uptake of B<sub>12</sub> (cobalamin) and iron-chelating siderophores (Shultis et al., 2006) potentially intertwining iron and B-vitamin acquisition (Wienhausen et al., unpublished). Further, the number of importers per genome, types of protein subcomponents, and ATP/ion requirements vary across plankton (Vitreschak et al., 2003; Rodionov et al., 2008; Eitinger et al., 2011; Rodionov et al., 2019) and the advantages of different configurations is unclear due to a lack of experimental testing.

Compared to importers, virtually nothing is known about B-vitamin exporters, which is striking considering net ‘provision’ of B-vitamins by plankton – including bacteria and algae – was first described in the mid-1900’s (Burkholder, 1963; Carlucci and Bowes, 1970; Haines and Guillard, 1974b). Some importers are proposed to function as exporters based on their occurrence in prototrophs or their low B-vitamin affinity (Jaehne and Slotboom, 2015; Rodionov et al., 2019). ‘Dual-functioning’ transport systems are a fascinating possibility but would require strict regulation to effectively export or import under appropriate conditions. Fluorescent tagging of B-vitamin/vitamins, as used to recently study importers (Anderson et al., 2016; Rosnow et al., 2018), and experiments with genetically engineered strains coupled with bioassay-based or chemical-based measurements of exported B-vitamins (Carlucci and Silbernagel, 1966; Bonnet et al., 2010) could help identify exporters (also importers) and associated export (also import) of vitamins or vitamers.

We posit that an improved understanding of importer and exporter functionality will elevate genome-based predictions of which plankton are key net ‘providers’ (providers of exogenous B-vitamin/vitamer) or ‘consumers’ (users of exogenous B-vitamin/vitamer), but also involved in widespread exchanges between plankton. Notably, recent isolate experiments highlight that predicting net ‘provision’ or ‘consumption’ is not always possible even with complete genome sequences (Paerl et al., 2017; Shelton et al., 2019; Wienhausen et al. unpublished). For example, co-culture experiments with *Escherichia coli* K-12 and *Vibrio anguillarum* PF430-3, two isolates with complete and



public genome sequences as well as arguably well-annotated B-vitamin metabolic pathways and transporters, showed exchange of vitamin B<sub>1</sub> (thiamin) and a precursor HMP (4-amino-5-hydroxymethyl-2-methylpyrimidine) but not thiazole precursor – and this was genetically unexplainable (Sathe et al., 2022). Experiments with marine plankton and genome surveys similarly highlight the uncertainty in predicting B-vitamin uptake and efflux (Rodionov et al., 2008; McRose et al., 2014; Paerl et al., 2018a; Paerl et al., 2018b).

Overall, unraveling the details of vitamin and vitamer transport holds great promise to aid predictions of marine plankton physiology, metabolism and interactions. It should be a future priority to investigate the functionality of characterized and uncharacterized transporter systems, but also associated cellular responses, e.g. synthesis and salvage pathways, motility, etc., tied to consumption or provision of B-vitamins/vitamer. Experiments with ‘model’ strains with complete genomes as well as synthetic communities are the easiest path forward to obtain information in these areas and ultimately increase our power to predict changes in community composition and activity (Follows and Dutkiewicz, 2010; Casey et al., 2022), and resolving niches and interdependency amongst marine plankton (D’Souza et al., 2018).

## 2. Disentangling B-Vitamin/Vitamer Exchange Between Microbes

Numerous organic molecules are exchanged ‘actively’ (e.g. exported) or ‘passively’ (e.g. lost *via* cell lysis) between microbes (D’Souza et al., 2018), including B-vitamins. Exchanges involving vitamins/vitamer and macronutrients are known; for example, bacteria providing B<sub>12</sub> to co-occurring algae and in turn receiving organic carbon (Haines and Guillard, 1974b; Croft et al., 2005; Kazamia et al., 2012; Durham et al., 2015).

Culture experiments have revealed the potential for plankton B-vitamin exchange while providing a ‘guiding light’ for investigating cellular level details behind B-vitamin exchange (see above) and interconnectivity between populations (Burkholder, 1963; Haines and Guillard, 1974a; Paerl et al., 2017; Cruz-López et al., 2018; Cooper et al., 2019; Wienhausen et al. unpublished) (**Figure 1**). Notably, it is unclear if specific vitamin/vitamer(s) are being shared in these experiments. Clarity is needed on whether vitamin or vitamer(s) or both are commonly exchanged and why, especially now that we know vitamers are useful for key marine plankton influencing key biogeochemistry and food webs (Helliwell et al., 2016; Gutowska et al., 2017; Paerl et al., 2018b; Wienhausen et al. in press).

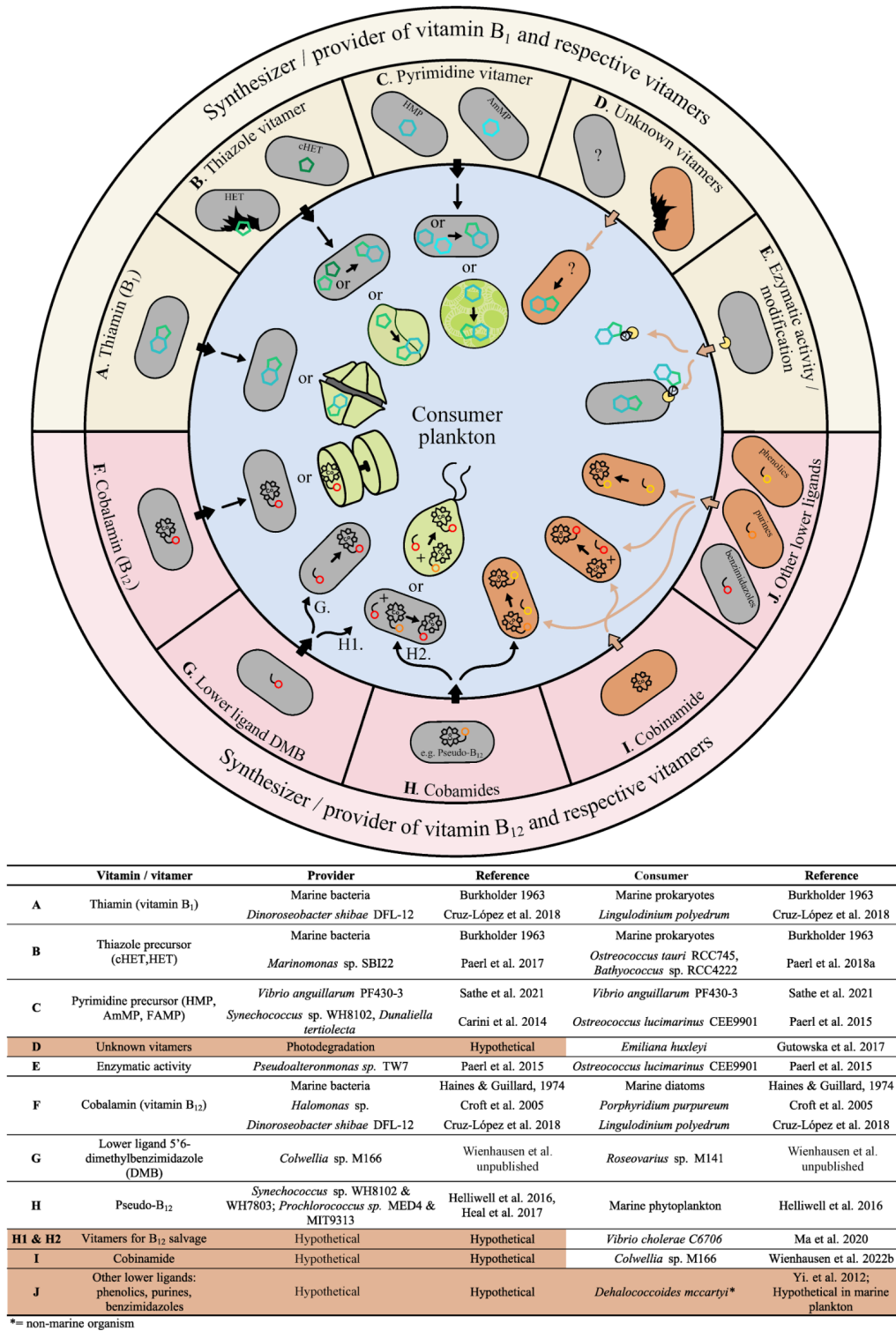
It is presently difficult to discern what cells are truly net ‘providers’ versus ‘consumers’ of B-vitamin(s) in the ocean. *De novo* synthesizers, auxotrophs salvaging vitamin from respective vitamers, and microbes modifying organics for other cellular needs (e.g. access to phosphate *via* alkaline phosphatase) all can be sources of vitamins/vitamer. Consumers are any cell capable of vitamin/vitamer uptake – whether or not they are B-vitamin auxotrophs (**Figure 1**). Genomic and transcriptomic efforts thus far have mainly focused on bacteria and algae, as well as vitamins B<sub>1</sub> and B<sub>12</sub>, leaving many unknowns about other B-vitamins and

the roles archaea and non-photosynthetic eukaryotes play as B-vitamin sources (Croft et al., 2006; Tang et al., 2010; Sañudo-Wilhelmy et al., 2014; Doxey et al., 2015; Poulson-Ellestad et al., 2016). Additionally, vitamin/vitamer ‘provision’ is not well predicted from genetic data (see section 1) (Sathe et al., 2022; Wienhausen et al. unpublished). Furthermore, the dynamic physical, biochemical, and biological variables in the ocean potentially alter B-vitamin exchange and concentrations (Carini et al., 2014; Gómez-Consarnau et al., 2018; Suffridge et al., 2020). Prokaryotes are traditionally considered B-vitamin ‘providers’, especially B<sub>12</sub> (Haines and Guillard, 1974b; Provasoli and Carlucci, 1974); however, recent findings indicate they may also be key ‘consumers’ (Koch et al., 2012). To understand this conundrum of microbial function as B-vitamin providers or consumers, we need to further disentangle what exchanges are possible *in situ*.

Prototrophs are the source of ‘new’, versus salvaged, vitamin to the ocean and thus are logical potential B-vitamin ‘providers’. However, differences in the extent of provision is likely – for example vitamin B<sub>1</sub> and pyrimidine precursors, rather than thiazole precursors, are shared among prokaryotes (Sathe et al., 2022) (**Figure 1**, see B, C). One complexity to ‘provision’ from prototrophs involves cyanobacteria, which are generally prototrophic for B-vitamins but importantly use and produce a specific form of B<sub>12</sub>, pseudo-B<sub>12</sub>, which is not bioavailable to most plankton (**Figure 1**, see H) (Helliwell et al., 2016; Heal et al., 2017). Prokaryotes and eukaryotes can remodel lower ligands of cobamides, a family of cobalt containing cofactors including B<sub>12</sub> and pseudo-B<sub>12</sub> (Helliwell et al., 2016; Ma et al., 2020). In this respect it is possible that the availability and cycling of lower ligands in the ocean (**Figure 1**, see H1, H2), e.g. benzimidazoles, purines and phenols, plays a more significant role than previously recognized (Yi et al., 2012; Men et al., 2014). We are only starting to understand how B<sub>12</sub>-vitamin/vitamer help to fulfill the needs of marine plankton and are involved in microbial exchange and how, for example, prophage-triggered lysis contributes to their release (Wienhausen et al. unpublished).

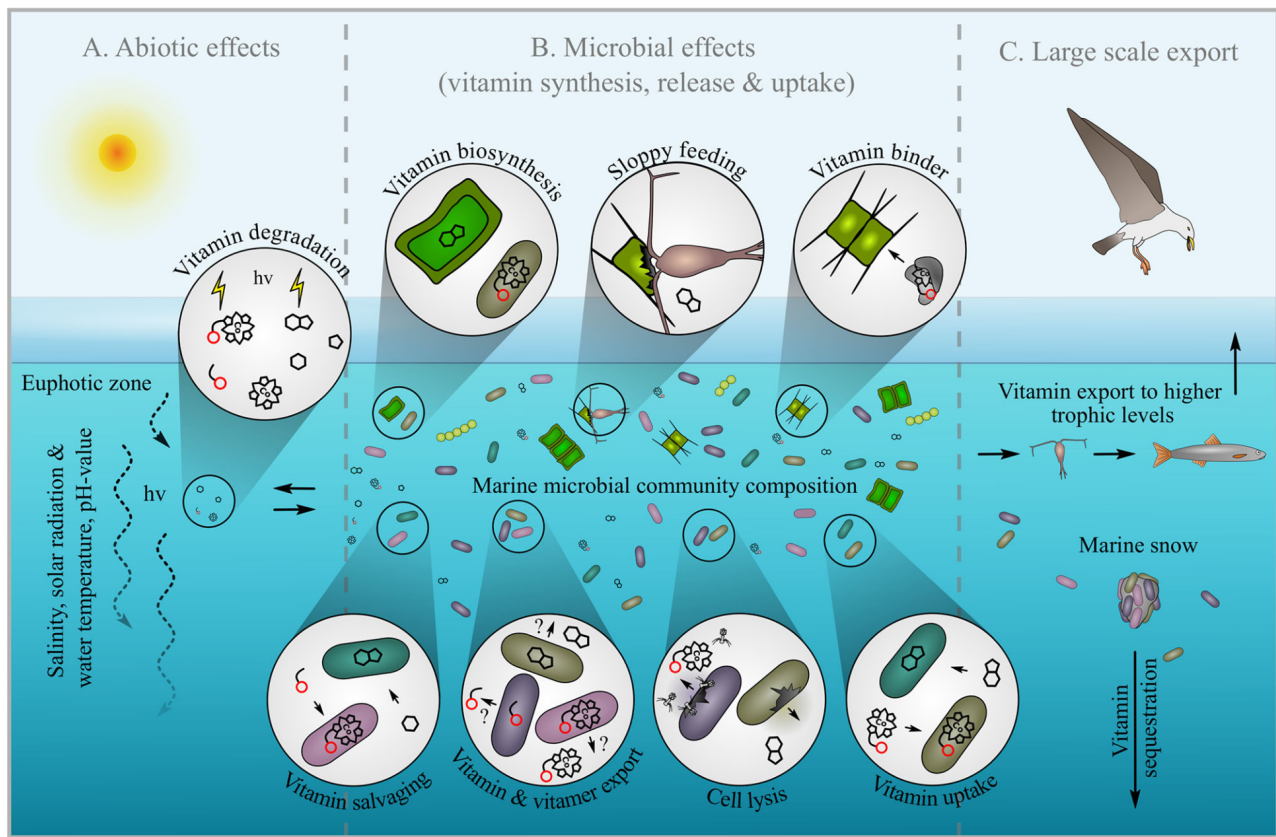
In the case of B<sub>12</sub> in particular, eukaryotes and prokaryotes compete for the same rare, yet pivotal cofactor, with the latter outnumbering the former. To ensure sufficient uptake, some phototrophic eukaryotes can release proteins that effectively bind B<sub>12</sub> (Provasoli and Carlucci, 1974; Pintner and Altmeyer, 1979; Bertrand et al., 2012). Protein binding has potentially far-reaching implications for B<sub>12</sub> availability and microbial interactions dependent on B<sub>12</sub> exchange, yet has received little recent attention. Non-marine studies also describe vitamin B<sub>1</sub> binding proteins produced by non-marine microorganisms (Itokawa et al., 1982), thus binding proteins may impact the availability of other B-vitamins in the ocean (**Figure 2B**).

Extracellular enzyme activity may also factor into recovering B-vitamins/vitamer and microbial exchange (**Figure 1E**). For example, phosphatase activity from co-occurring bacteria can give select algae access to phosphorylated vitamin B<sub>1</sub> (via dephosphorylation), which is not useful for the algae alone (Paerl et al., 2015). Other B-vitamins (e.g. vitamin B<sub>6</sub>) and vitamers (e.g. HMP), and possibly yet to be identified vitamers



**FIGURE 1 |** B-vitamin/vitamer exchange amongst marine plankton. The outer ring illustrates prokaryotes that synthesize and provide vitamins or vitamers. Examples of vitamin B<sub>1</sub> and respective vitamers (**A–E**) are shown in the yellow semicircle and examples of vitamin B<sub>12</sub> and respective vitamers (**F–J**) are shown in the red semicircle. The inner blue circle shows prokaryotic and eukaryotic plankton recipients that can use vitamin B<sub>1</sub> and respective vitamers (**A–E**) or vitamin B<sub>12</sub> and respective vitamers (**F–J**). Details on (**A–J**), including citations and representative organisms displaying each trait, are provided in the bottom grid. Provider and consumer microbial traits that are hypothetical or have not yet been verified in the marine environment are highlighted in orange and noted accordingly.





**FIGURE 2 |** B-vitamin cycle in the pelagic ocean. The left section **(A)** illustrates abiotic factors that can affect the stability of B-vitamins including salinity, solar radiation, water temperature and pH. Microbial processes describing vitamin synthesis and salvaging as well as vitamin release and uptake are shown in the middle section **(B)**. Potential routes of large-scale B-vitamin export are depicted in the right section including transfer up the marine food web to higher trophic levels and sinking of B-vitamin rich marine snow **(C)**.

are phosphorylated through cellular biosynthesis (Figure 2A) (Jurgenson et al., 2009; Parra et al., 2018); thus, their use and exchange could be similarly impacted by extracellular enzyme activity.

Future research should focus on disentangling vitamin/vitamer exchange in (1) environmentally relevant co-cultures, (2) defined plankton consortia with multiple B-vitamin requirements and (3) experiments considering the impacts of enzymatic activity. A more complete view of exchanges will likely advance understanding of co-evolution in the ocean, from tight-proximity symbioses (Croft et al., 2005; Blifernez-Klassen et al., 2021) or distant plankton exchanges, which are more prevalent in the ocean (Droop, 2007).

### 3. Marine B-Vitamin Cycling on the Ecosystem Scale

The physical, chemical and biological properties of the ocean are unique compared to other natural systems (e.g. soils, human gut), and both biotic and abiotic factors are anticipated to uniquely impact B-vitamin availability. Abiotic degradation of B-vitamins/vitamers is expected but at what rates? Experimental evidence suggests B-

vitamin degradation products have a longer half-life than intact vitamins at least on the basis of light exposure (Carlucci et al., 1969; Gutowska et al., 2017). In non-marine experiments, B-vitamins degrade under elevated temperature, pH, irradiance, and metal concentrations (Dwivedi and Arnold, 1973; Combs and McClung, 2016). Light and temperature are known to degrade B<sub>1</sub> and B<sub>12</sub> in seawater (Gold, 1968; Carlucci et al., 1969). Intriguing recent evidence indicates some algae may be better adapted to use photodegraded vitamin versus non-degraded vitamin (Gutowska et al., 2017). Alkaline conditions degrade B-vitamins (Jenkins et al., 2007), but in the well-buffered pelagic ocean water, high pH (>10) would have to exist in particle or cell-associated microenvironments. In recent years considerable progress has been made to quantify vitamers (including degradation products) from seawater (Heal, 2014; Suffridge et al., 2017; Longnecker et al., 2018; Suffridge et al., 2020; Wienhausen et al. unpublished), but in several cases it is unclear if abiotic and/or biotic processes were responsible for the presence of vitamers in the ocean. A better understanding of the effects of various abiotic factors, including temperature, acidification or solar radiation on B-vitamin/vitamer stability is needed, especially under climate change scenarios (Figure 2A).

In the pelagic ocean, acquisition of dissolved B-vitamins is vital for microbial function and survival, but the influence of community composition on B-vitamin availability remains unclear. Mesocosm experiments indicate that microbial growth is limited due to B-vitamin deficiency (e.g., B<sub>12</sub>) in different oceanic provinces (Bertrand et al., 2007; Joglar et al., 2020; Wienhausen et al., in press) and B-vitamin (B<sub>1</sub>, B<sub>7</sub>, B<sub>12</sub>) concentrations in seawater can be below those required for microbial growth (Sañudo-Wilhelmy, 2012; Johnson et al., 2021). Putative microbial ‘providers’ and ‘consumers’ of individual B-vitamins have been identified based on genome-based predictions of auxotrophy/prototrophy (Sañudo-Wilhelmy et al., 2014), but as discussed above, these assumptions must be approached with caution. Greater understanding on these fronts is needed in order to begin classifying the availability of dissolved B-vitamins in different oceanic provinces (Longhurst, 2010; Reygondeau et al., 2018). For example, current knowledge suggests cyanobacteria are a vast source of pseudo-B<sub>12</sub> in tropical to subtropical provinces and the fraction of B<sub>12</sub> prototrophic bacteria decreases sharply towards the poles (Doxey et al., 2015; Heal et al., 2017; Wienhausen et al., unpublished). In contrast, archaea appear to be significant sources of B<sub>12</sub> in the deep ocean (Doxey et al., 2015). There is much left to resolve in this area and some consideration of activity along with biogeography should be taken into account – e.g. transcript abundance as an indicator of metabolic activity (Gómez-Consarnau et al., 2018). Additionally, the amount of vitamins/vitamins synthesized and ‘provided’ per cell (or biomass) is crucial for estimating vitamin availability in the pelagic ocean. Limited estimates of vitamins present or released per cell are available (Bonnet et al., 2010; Carini et al., 2014; Paerl et al., 2015; Gutowska et al., 2017; Suffridge et al., 2017). Obtaining such information would help constrain estimates of B-vitamin exchange as well as change in plankton communities *in situ* (Teeling et al., 2012; Suffridge et al., 2018).

Beyond cell export, B-vitamins are expected to enter dissolved seawater *via* cell mortality, especially viral lysis and ‘sloppy feeding’ by grazers (Fuhrman, 1999; Wilhelm and Suttle, 1999; Møller et al., 2003; Poulson-Ellestad et al., 2016). About half of all marine bacteria are lysed by phages, resulting in the release of dissolved organic matter (DOM), including vitamins, *via* the ‘viral shunt’ (Fuhrman, 1999; Breitbart et al., 2018). Another caveat is that B-vitamin liberated *via* mortality may be bound to proteins (as in cells) or other organics (Provasoli and Carlucci, 1974; Itokawa et al., 1982) rendering it inaccessible (**Figure 2B**). How much B-vitamin in seawater is accounted for by viral lysis or grazing is not known, and will require chemical (mass spectrometry) (Suffridge et al., 2017) and biological assessments (bioassays) (Carlucci and Silbernagel, 1966) to fully address.

Zooplankton and ‘mixotrophic’ algae play an additional key role in B-vitamin cycling by directly contributing to transfer of vitamins to higher trophic levels, and this also requires greater exploration. In the case of B<sub>1</sub> for example, intracellular concentrations within different zooplankton species can be species-specific, vary seasonally and spatially within organisms of the same genus (Fridolfsson et al., 2018). Differences in B-vitamin availability per biomass within steps of food webs can have dramatic consequences at higher trophic levels, such as birds and fish, where it has been shown that B<sub>1</sub> deficiency can

severely increase mortality and breeding failure (Balk, 2009; Keinänen et al., 2012). More biomass normalized B-vitamin production data for organisms at different trophic levels will enable better tuning of trophic transfer models and likely improved predictions of ecosystem-wide B-vitamin budgets (Ejsmond et al., 2019). Interestingly, grazing may be impacted by B-vitamin availability (Anderson et al., 2018), thus trophic transfer of vitamins as well as other nutrients may be impacted by vitamin availability. B-vitamin trophic transfer is potentially reduced *via* export of vitamin-rich particles, e.g. marine snow (Alldredge and Silver, 1988), to the ocean interior. Another point of future exploration is the B-vitamin content of recently formed particles, its importance in supporting free and particle-associated communities and metabolism, especially in the deep sea (**Figure 2C**).

## FUTURE DIRECTIONS

We recommend culture or ‘bottle’ experiments that allow controlled examination of cell responses to changes in B-vitamin availability or exchange, abiotic degradation experiments, as well as implementing compound tracing (e.g. isotopic, fluorometric) methods and quantification methods (e.g. liquid chromatography mass spectrometry) to fill the key knowledge gaps highlighted above. A last suggestion is that future research view B-vitamin cycling more through a climate change ‘lens’ – especially given that predicted ocean change includes alteration of temperature, irradiance intensity and pH all of which are known to impact the stability of B-vitamins (Combs and McClung, 2016). Overall, numerous exciting discoveries are on the horizon related to marine B-vitamin cycling and are readily achievable with straightforward experimentation.

## AUTHOR CONTRIBUTIONS

GW, MB, and RP all contributed to writing of the perspective. GW constructed illustrations with feedback from MB and RP. All authors contributed to the article and approved the submitted version

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