



# Upside-Down but Headed in the Right Direction: Review of the Highly Versatile *Cassiopea xamachana* System

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**Specialty section:**

This article was submitted to  
Coevolution,  
a section of the journal  
Frontiers in Ecology and Evolution

**Received:** 29 January 2018

**Accepted:** 20 March 2018

**Published:** 09 April 2018

**Citation:**

Ohdera AH, Abrams MJ, Ames CL,  
Baker DM, Suescún-Bolívar LP,  
Collins AG, Freeman CJ,  
Gamero-Mora E, Goulet TL,  
Hofmann DK, Jaimes-Becerra A,  
Long PF, Marques AC, Miller LA,  
Mydlarz LD, Morandini AC,  
Newkirk CR, Putri SP, Samson JE,  
Stampar SN, Steinworth B,  
Templeman M, Thomé PE, Vlok M,  
Woodley CM, Wong JC,  
Martindale MQ, Fitt WK and Medina M  
(2018) Upside-Down but Headed in  
the Right Direction: Review of the  
Highly Versatile *Cassiopea xamachana*  
System. *Front. Ecol. Evol.* 6:35.  
doi: 10.3389/fevo.2018.00035

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The upside-down jellyfish *Cassiopea xamachana* (Scyphozoa: Rhizostomeae) has been predominantly studied to understand its interaction with the endosymbiotic dinoflagellate algae *Symbiodinium*. As an easily culturable and tractable cnidarian model, it is an attractive alternative to stony corals to understanding the mechanisms driving establishment and maintenance of symbiosis. *Cassiopea* is also unique in requiring the symbiont in order to complete its transition to the adult stage, thereby providing an excellent model to understand symbiosis-driven development and evolution. Recently, the *Cassiopea* research system has gained interest beyond symbiosis in fields related to embryology, climate ecology, behavior, and more. With these developments, resources

including genomes, transcriptomes, and laboratory protocols are steadily increasing. This review provides an overview of the broad range of interdisciplinary research that has utilized the *Cassiopea* model and highlights the advantages of using the model for future research.

**Keywords:** jellyfish, symbiosis, toxinology, sleep, venom, scyphozoan systematics, bioindicator

## INTRODUCTION

The upside-down jellyfish *Cassiopea* is a benthic scyphozoan (Rhizostomeae) commonly found in tropical and sub-tropical shallow coastal ecosystems, such as mangroves and seagrass beds. *Cassiopea* spp. are unique among scyphomedusae in that their characteristic flat exumbrella rests on the sea bottom, while their convex subumbrella and oral arms face upwards. High light penetrance is important for species within this genus, as the jellyfish hosts one or more photosynthetic dinoflagellate species of the genus *Symbiodinium* (Hofmann et al., 1996; Lampert, 2016). Similar to their coral relatives, nutrient exchange is a key component supporting this cnidarian-dinoflagellate mutualism (Hofmann and Kremer, 1981; Welsh et al., 2009; Freeman et al., 2016). In addition, *Cassiopea* spp. rely on the symbionts as a developmental trigger (Hofmann et al., 1978; Colley and Trench, 1985). A fascination with these requisite traits of the upside-down jellyfish has fueled studies on the *Cassiopea*-*Symbiodinium* interaction since the 1980s (see recent review by Lampert, 2016). While its efficacy as a system for symbiosis research is well known in the literature, *Cassiopea* is gaining momentum as a model species in other areas. In mathematics, the symmetric morphology and relatively simple neuromuscular system of the upside-down jellyfish make it an ideal system from which to develop computational fluid dynamic and neuromechanical models (Passano, 2004; Hamlet et al., 2011; Santhanakrishnan et al., 2012). Additionally, *Cassiopea* has been presented as a possible model organism for the study of behavioral biology as highlighted by recent developments with sleep behavior (Nath et al., 2017; **Figure 1**). Likewise, this jellyfish genus has been gaining traction as a biomonitor/bioindicator species, with applications for coastal ecosystem management (Templeman and Kingsford, 2012; Epstein et al., 2016; Klein et al., 2016a, 2017). The relative simplicity of culturing *Cassiopea* polyps and medusae makes this genus a highly amenable laboratory system. With newly established *Cassiopea xamachana* clonal laboratory lines, and recent advances in affordable genomics tools giving way to draft transcriptome and genome assemblies, the upside-down jellyfish is an appropriate candidate as a model organism. Here, we review *Cassiopea* research conducted to date and discuss future directions of this highly valuable study system.

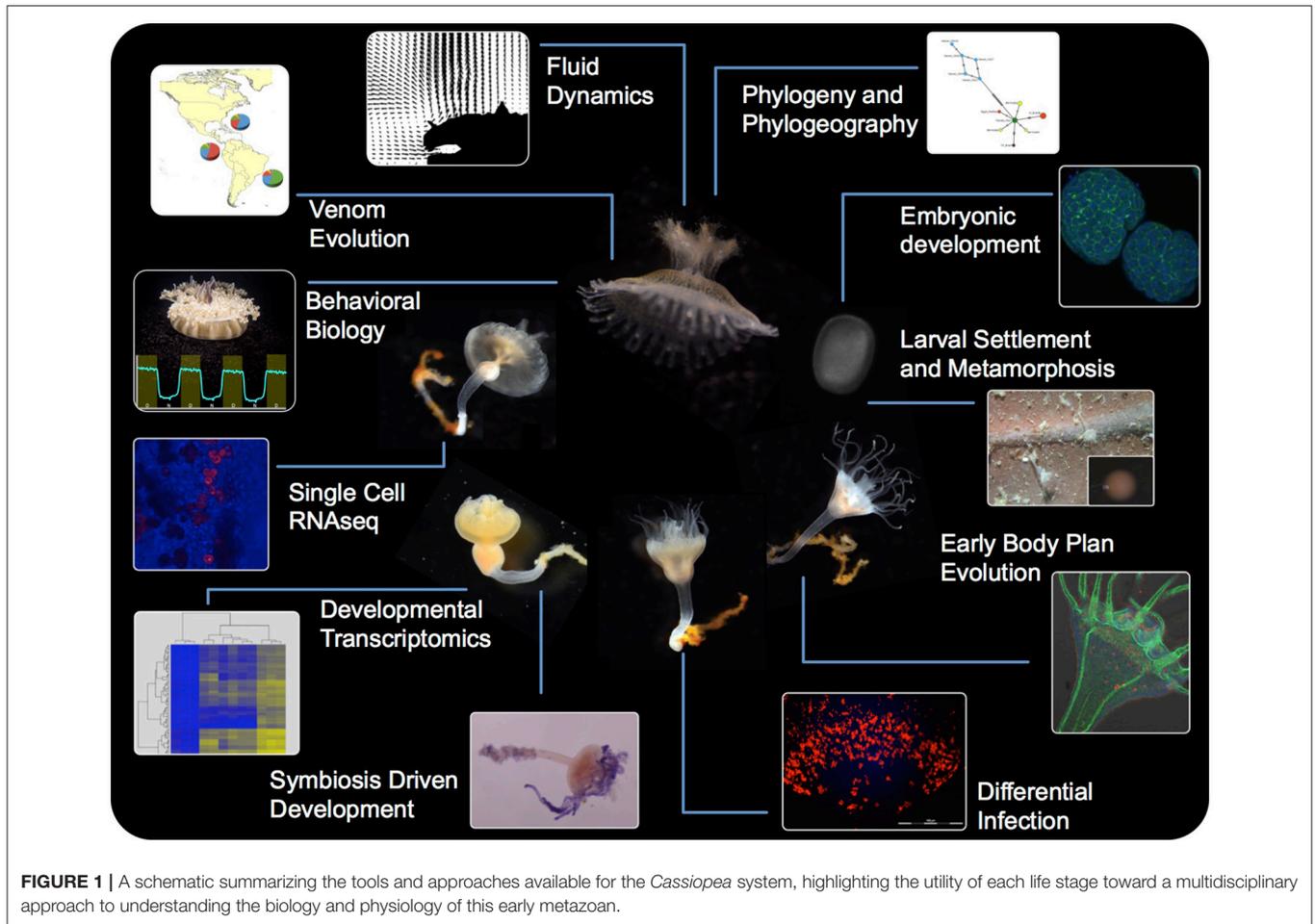
## EVOLUTION AND PHYLOGENETICS

The first species of the genus *Cassiopea* was described from the Caribbean as *Medusa frondosa* by Pallas (1774), and just one year later a second species from the Red Sea was described as

*Medusa andromeda* (published as a *post mortem* work; figures published only in Forskål (1776). The generic name *Cassiopea* was proposed for all jellyfish with foliaceous appendages in 1810 (Péron and Lesueur, 1810). Members of the genus *Cassiopea* were treated as a family by Tilesius (1831), and the current spelling appeared ~30 years later (Agassiz, 1862). The species-level relationships of the genus *Cassiopea* are still unresolved since most of the taxonomic studies are based on overlapping, plastic, and polymorphic features (**Table 1**; Mayer, 1910; Kramp, 1961). This is confounded by vague species descriptions with species diagnoses that are descriptive rather than comparative, although morphology has been useful in distinguishing some congeneric species, i.e., *Cassiopea frondosa*. In total, 24 nominal species, and varieties thereof, have been proposed to date (**Table 1**), but only 10 species are presently considered to be valid based on molecular data (Holland et al., 2004; Arai et al., 2017; Morandini et al., 2017). These studies show that populations of *C. xamachana* are potential introduction of *Cassiopea andromeda* from the Red Sea, thereby grouping the species into a single lineage. These species designations, which are based on kimura 2-parameter pairwise distance, fall within previous estimations for other scyphozoans, ranging from 0.00 to 0.034 for conspecifics, and 0.102–0.234 for congenics (Holland et al., 2004; Ortman et al., 2010; Gómez Daglio and Dawson, 2017). Analyses with expanded taxon sampling (Bayha et al., 2010; Kayal et al., 2013, 2017) have placed the monogeneric *Cassiopea* within the family Cassiopeidae, in an unstable position within the clade Kolpophorae, along with representatives of Mastigiidae, Thysanostomatidae, Versurigiidae, and Cepheidae (**Figure 2**). The Kolpophorae belongs to the order Rhizostomeae, a well-supported clade derived from within the scyphozoan order Semaestomeae (Bayha et al., 2010; Kayal et al., 2013).

While the polyp stage and strobilation of *C. xamachana*, as well as the polyp stage of *C. frondosa*, were described by Bigelow (Bigelow, 1892, 1893), a complete description of the life cycle of *C. xamachana* did not appear in the literature until almost a decade later (Bigelow, 1900). Additional details of the life cycle were later published on a population of *C. andromeda* from Al-Ghardaqa (Red Sea) (Gohar and Eisawy, 1960). Although the morphology of *Cassiopea* is unique and known only from extant forms, a fossil dated to the Solnhofen formation lagerstätte (Jurassic, *Myogramma speciosum*) has a similar arrangement of what appears to be the muscular system (Maas, 1902).

Moving forward, enhanced taxon sampling and character analyses by multi-omics methods on a broad geographical scale will facilitate rigorous testing of phylogenetic hypotheses and assessment of genetic richness related to cryptic species,



thereby allowing research on different *Cassiopea* systems from a comparative evolutionary perspective.

## LIFE HISTORY

*Cassiopea* spp. are gonochoristic brooders, with fixed sex determination, although a case of hermaphroditism has been reported from Hawai'i (Hofmann and Hadfield, 2002). Fertilization has been reported to occur within the gastrovascular cavity of the female (Smith, 1936). The embryos pass from the gastrovascular cavity through the brachial canal out of the secondary mouths, and are subsequently deposited onto the oral disc. Because motile settlement-competent planulae can be found attached to the female's oral disc at any given point, the duration of attachment (i.e., brooding) in the absence of outside disturbance is unknown. Cleavage begins ~1–2 h after the fertilized eggs are visible on the oral disc, and then round, ciliated embryos are present 48 h post-fertilization. By 96 h post-fertilization, elongate ovoid planulae, rotating around the longitudinal axis, swim with clear directionality and are capable of settling and becoming polyps. While a detailed characterization of early embryonic development in *Cassiopea* is yet to be done, developmental timing appears to be temperature

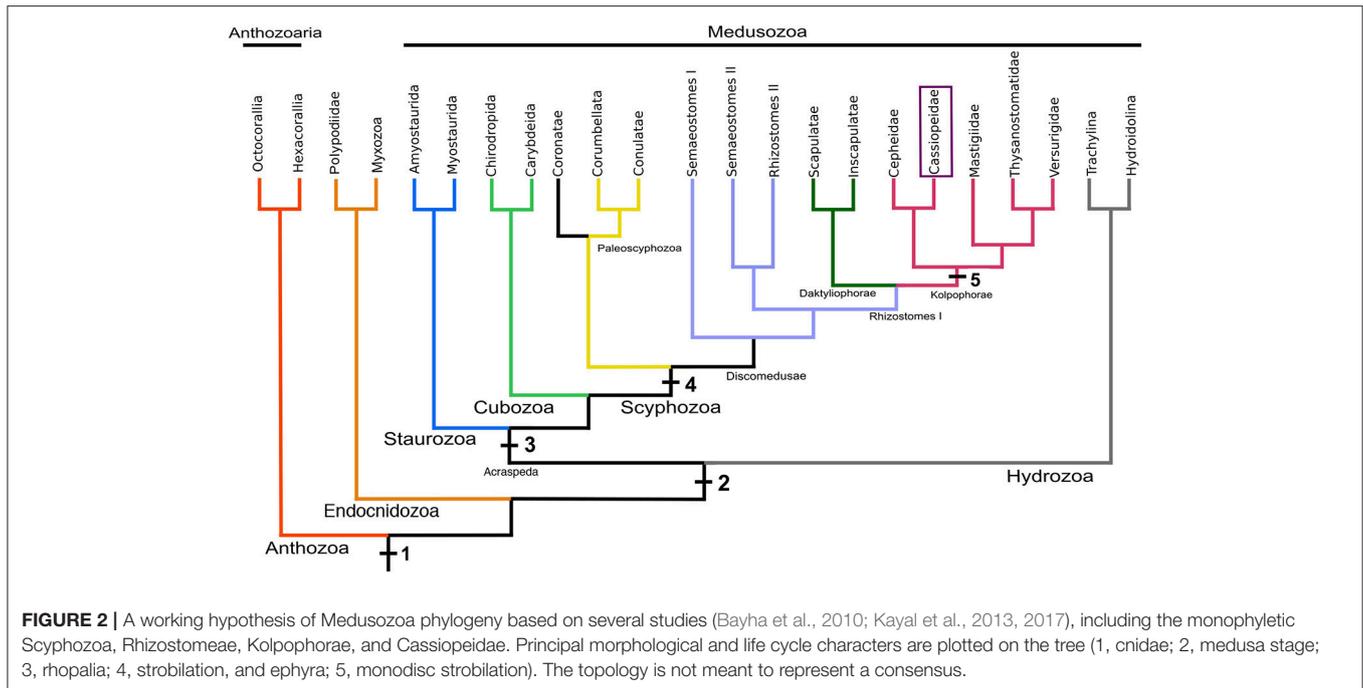
dependent and planula morphology has been well described (Martin and Chia, 1982).

Hox genes are present in *C. xamachana* (Kuhn et al., 1999; Ferrier and Holland, 2001), and work on other cnidarians suggests these may be involved in patterning the oral-aboral axis. In both the anthozoan *Nematostella vectensis* and the hydrozoan *Clytia hemisphaerica*, planula, and polyp stages show differential Hox expression along the oral-aboral axis (Ryan et al., 2007; Chiori et al., 2009). Patterning of the medusa body form remains a more complicated question, as expression of some Hox genes were localized to sensory structures and the bell (Chiori et al., 2009), while others were expressed specifically in oral endoderm. In addition to Hox expression during development, homeobox genes are active during cnidarian regeneration (Schummer et al., 1992) and *Cassiopea* has gained some attention as a model for regeneration (Cary, 1916; Curtis and Cowden, 1974; Polteva, 1985). Of particular note, all *Cassiopea* life stages show telomerase activity, with potential elongation of the telomere during the medusa stage (Ojimi et al., 2009; Ojimi and Hidaka, 2010), paving the way for additional research in the genetic mechanisms of regeneration and longevity in non-bilaterian organisms. Future research in *Cassiopea* development incorporating genomics, transcriptomics, metabolomics, and *in situ* hybridization will

**TABLE 1** | Morphological data on valid *Cassiopea* species, modified from Morandini et al. (2017).

Species	Size (cm)	Exumbrella shape	Lappets in each paramere	Rhopalia	Mouth arms	Appendages	Type locality	Distribution	Life cycle known	Bioinvasion	GenBank*
<i>C. andromeda</i> (Forskål, 1775)	10–12	flat	1–10	12–19 (16)	4–6 branches	n small, 5 or more large, club shaped vesicles	Red Sea	Western Atlantic, North Pacific, Mediterranean Sea, Indo-Pacific	Yes <sup>+</sup>	Yes <sup>1</sup>	Yes
<i>C. depressa</i> (Haeckel, 1880)	10–12	flat	9	16	6–8 branches	n small clubs	Madagascar, Mozambique	Madagascar and off coast of Mozambique, E. Africa	No	No	No
<i>C. frondosa</i> (Pallas, 1774)	12–26	flat	5	12	bifurcated at their ends with short, pinnate side branches	30–40 small leaf shaped vesicles	West Indies, Caribbean	West Indies to Florida	No	No	Yes
<i>C. maremetens</i> (Gershwin et al., 2010)	2–20	broad, shallow, aboral concavity	4	19	4–6 with distal bifurcation	1–2 central, 1 base arm, 1 tip arm	Lake Magellan, Australia	Queensland, Australia	No	No	No
<i>C. medusa</i> (Light, 1914)	26	flat	7	17	n branches (3 main distal)	n small/large	Culion Bay, Philippines	Hawaii & Philippines	No	Yes <sup>2</sup>	No
<i>C. mertensi</i> (Brandt, 1835)	10–12	rounded without a concavity	8	16	8–12 main branches	n large clubs	Kosrae Island, Micronesia	Caroline Islands & Hawaii	No	Yes <sup>3</sup>	No
<i>C. ndrosia</i> (Agassiz and Mayer, 1899)	5	concave	4	18–22	6–12 main branches	n small leaf shaped	Suva, Fiji	Australia & Fiji	No	No	No
<i>C. ornata</i> (Haeckel, 1880)	10–12	flat	5	16	9–12 side branches	n small clubs	Palau, Papua New Guinea	Malay Archipelago	No	No	Yes
<i>C. vanderhorsti</i> (Stasny, 1922)	17	flatly rounded, with a low central dome	3–5	14–18	pinnately dichotomous	n small and few large vesicles	Caracas Bay, Curaçao	Caracas Bay, Curaçao	No	No	No
<i>C. xamachana</i> (Bigelow, 1892)	15	concave	5	11–23 (16)	10–15 alternate branches	large and small ribbon-like filaments	Kingston Harbor, Jamaica	West Indies to Florida	Yes <sup>–</sup>	No	Yes

Holland et al. (2004) <sup>2</sup> Doty (1961) <sup>3</sup> Uchida (1970) Gohar and Ehsawy (1960) Bigelow (1900).



allow further characterization of pre-swimming development, particularly timing and stereotype of gastrulation, and precise identification of morphological characteristics denoting settlement competency. The multi-omics approach will lay the foundations for describing the developmental genes regulating the life history of these scyphozoans and generate testable hypotheses toward understanding the evolution of cnidarian life cycles and bauplans.

## Bud Morphogenesis

Polyps of the genus *Cassiopea* are capable of producing planuloid buds 3–4 mm in length via evagination from the aboral region of the calyx (Van Leishout and Martin, 1992; **Figure 3**). Bud formation and detachment can occur at a relatively rapid rate, with buds released as frequently as 2–3 per day. Progenitor ectodermal cells are recruited distally and asymmetrically from the site of bud morphogenesis rather than produced by a mitotically active population of cells (Hofmann and Honegger, 1990; Hofmann and Gottlieb, 1991). Planuloid buds form with their future oral pole most proximal to the body. The most distal part of the bud is the future aboral pole, which after detachment will be the leading pole of the swimming bud and the stalk of the future polyp (Curtis and Cowden, 1971). Within 24 h, settled buds will develop a hypostome and up to 16 tentacles, thereby providing the newly developed polyps with the capacity to capture prey. Head (calyx and tentacles) and stalk formation is contingent on settlement to a substrate, with a head-morphogenesis inhibiting signal potentially generated from the aboral pole of the swimming bud (Neumann, 1980). It has been reported that oral halves of transversely bisected buds properly developed the hypostome and tentacles but lacked a stalk, while the aboral halves developed into full

scyphistomae (Curtis and Cowden, 1971; Neumann, 1980). Further, treatment of the oral fragment with bud homogenate as well as PKC inhibitors (psychosine, chelerythrine) showed inhibitory effects to head development (Thieme and Hofmann, 2003a,b), suggesting the important involvement of PKC in bud and larval metamorphosis (Fleck and Bischoff, 1992). Conversely, treatments with canathadrin, a serine/threonine protein phosphatase inhibitor, induced development of the head and stalk in scyphistomae, while methionine, homocysteine, trigonelline, nicotinic acid, and cycloleucine treatments all inhibited morphogenesis (Kehls et al., 1999).

## Settlement and Metamorphosis

Induction of settlement and metamorphosis in cnidarian species, including *Cassiopea* spp., is contingent on the presence of certain types of bacteria (Hofmann et al., 1978; Neumann, 1979; Leitz, 1997; Vermeij et al., 2009). Both larvae and planuloid buds of *Cassiopea* spp. settle and metamorphose in response to bacterial biofilm, including *Vibrio* sp. isolated from an *Artemia* culture (Hofmann et al., 1978). While the isolated *Vibrio* sp. showed toxic effects on polyp development, a metabolite (1–10 kDa) that was isolated from the bacteria induced settlement and metamorphosis of *Cassiopea* planulae (Neumann, 1979). A cholera toxin isolated from *Vibrio cholerae* was also inductive (Wolk et al., 1985). Collagen digestion by *Vibrio alginolyticus* also led to the production of inductive fractions, suggesting the involvement of a peptidic cue in polyp development (Hofmann and Brand, 1987). The discovery that certain small molecules and peptides are involved in polyp metamorphosis has led to the design of a synthetic peptide (GPGGPA) with settlement and metamorphosis inductive capacities (Fleck, 1998).



**FIGURE 3** | A *Cassiopea xamachana* polyp with a planuloid bud developing asexually from the aboral region of the calyx.

Research efforts attempting to isolate a peptidic cue from *Cassiopea*'s natural substrate, degraded mangrove leaves, resulted in extraction of several bioactive fractions, one of which contained a proline-rich 5.8 kDa peptide capable of inducing settlement and metamorphosis, although the precise amino acid sequence of this peptide or other natural cues have yet to be determined (Fleck and Fitt, 1999; Fleck et al., 1999). While cnidarian species have been shown to settle and metamorphose in response to mono-culture biofilm of multiple bacterial taxa (Tran and Hadfield, 2011), the exact underlying mechanism allowing planulae to react to multiple microbial cues has yet to be fully explored. Variation in induction response to artificial inducers (inorganic ions, phorbol esters, diacylglycerols, tetradecanoyl-phorbol-13 acetate) has been observed between hydrozoan and scyphozoan species (Müller, 1973; Henning et al., 1996; Siefker et al., 2000). The difference in induction response to artificial inducers noted between the moon jellyfish *Aurelia aurita* and *C. xamachana* (Fitt et al., 1987; Siefker et al., 2000), for example, are suggestive of potentially differing mechanisms of settlement induction. The evolution of cue specificity and signal transduction mechanisms of cnidarian larvae, and more generally invertebrate larvae, remains a topic requiring further research. The current understanding of *Cassiopea* species diversity and geographic distribution, coupled with the availability of several lab cultures, offers avenues to conduct comparative studies on the induction response of planulae to both natural and synthetic settlement inducers.

### **Cassiopea-Symbiodinium Symbiosis**

In many scyphozoans, the transition from polyp to medusa, known as strobilation, can be triggered by temperature and other exogenous cues (Spangenberg, 1965; Loeb, 1973; Holst, 2012). Strikingly, strobilation in *Cassiopea* requires colonization by the endosymbiont *Symbiodinium* spp. (Gohar and Eisawy,

1960; Hofmann et al., 1996). Without colonization, polyps will not undergo strobilation, although a single strobilation event in aposymbiotic polyps has been reported by Rahat and Adar (1980). *Cassiopea* spp. are monodisc strobilating scyphozoans, producing a single ephyra at each strobilation event. Strobilation generally occurs over several days, with the first few days characterized by a reduction in tentacle length (due to absorption), followed by the development of a disc-like apical structure bearing rhopalia and a medusoid form; shortly following is constriction by the polyp body resulting in release of the ephyra (Ludwig, 1969; Hofmann et al., 1978). Colonization of the polyp by the symbiont (i.e., dinoflagellate), and subsequent strobilation of an ephyra, happens in several discrete stages. The colonization process begins when symbionts enter the polyp through the mouth and are then phagocytosed by the gastroderm (Colley and Trench, 1983; Fitt and Trench, 1983). Successful colonization of cnidarian cells requires suppression of the host immune response, thereby revealing a link between symbiosis and innate immunity (Miller et al., 2007; Kvennefors et al., 2008). Along with other cnidarians, jellyfish show evidence of producing antimicrobial peptides that indicate their ability to identify between self and non-self (Rinkevich, 2004; Ovchinnikova et al., 2006; Bosch, 2008). This ability would be useful in regulating the host microbial composition as well as symbiont colonization and proliferation, a topic that has garnered significant attention and will benefit from the development of the *Cassiopea-Symbiodinium* research system (Detournay et al., 2012; Neubauer et al., 2016, 2017).

Events leading to successful colonization post-phagocytosis can be identified by the relative position of the algae within the phagocytosing cell (Colley and Trench, 1985). Initially, symbionts can be found toward the apical end of phagocytic cells and the basal end by day 3 post-entry. *Symbiodinium* cells that are unable to migrate basally are destroyed by lysosomal fusion. By day 8, host cells containing successful symbionts detach and migrate into the mesoglea where proliferation of symbiont-containing host-cells subsequently occurs (Colley and Trench, 1985). Strobilation takes place ~3 weeks later, depending on several factors including the symbiont species, temperature and food intake (Fitt and Costley, 1998). While the precise cue(s) responsible for initiation of strobilation is unknown, inhibition of photosynthesis with 3-(3,4-dichlorophenyl)-1,1-dimethylurea (DCMU) results in continuation of the process, albeit at lower rates (Hofmann and Kremer, 1981). In a non-symbiotic scyphozoan, *A. aurita*, initiation of strobilation was found to involve genes from the retinoic acid pathway (Fuchs et al., 2014; Brekhman et al., 2015). In contrast to *A. aurita*, treatment of *Cassiopea* polyps with retinoic acid does not result in strobilation (Silverstone et al., 1977; Pierce, 2005; Cabrales-Arellano et al., 2017). Conversely, indomethacin, a drug with structural resemblance to a peptide involved in strobilation in *Aurelia* induces metamorphosis of *C. xamachana* polyps to the mature medusa form (Kuniyoshi et al., 2012; Cabrales-Arellano et al., 2017). This observation suggests that while some aspects of the strobilation mechanism might be shared across Scyphozoa (Helm and Dunn, 2017; Yamamori et al., 2017), the evolution of symbiosis within members of the Rhizostomae may have resulted

in co-option of other pathways as a developmental trigger. With the availability of transcriptome and genome level sequence data awaiting extensive query, *Cassiopea* holds promise as an exciting system for the study of symbiosis-mediated development, as well the mechanisms involved in host colonization by its symbionts.

## NUTRITIONAL REQUIREMENTS

For symbiotic cnidarians, the essential nature of the symbiotic relationship strongly suggests that heterotrophic feeding from the surrounding waters may not provide nutrients sufficient to cover the carbohydrate and lipids needed for medusa metamorphosis, growth, and sexual reproduction. A major gap in our knowledge of algal-cnidarian symbiosis has been the understanding of the mechanisms underlying the biosynthesis and regulation of carbon flow from symbiont to host (Yellowlees et al., 2008; Davy et al., 2012), and the uptake of such carbon compounds by the host partner. In this context, identifying the chemical form of photosynthates or so-called “mobile compounds” (Trench, 1971; Venn et al., 2008) has proven challenging, although it most likely involves complex metabolic modifications. In other well-known examples of algal-cnidarian symbiotic relationships in scleractinian corals, glycerol is the dominant photosynthate produced (Gattuso et al., 1993; Hagedorn et al., 2010), while glucose is the dominant photosynthate in the sea anemone genus *Exaiptasia* (formerly *Aiptasia*) (Burriesci et al., 2012; Molina et al., 2017). Early  $^{14}\text{C}$  (radiocarbon) labeling studies in *C. andromeda* showed that glucose and glycerol were the only two free metabolites detected after short term labeling (3–60 min) in medusa tissue for samples incubated in the light (Hofmann and Kremer, 1981). These experiments showed that labeled glycerol disappeared in <30 min, likely through utilization in lipid synthesis, as suggested by the authors; these findings were later corroborated with findings of a similar study on the sea anemone *Exaiptasia* (Davy and Cook, 2001). *In vivo* carbon fixation by the symbiont is highly efficient in *C. xamachana*, with rates exceeding daily respiration requirements of the host, supporting a growth rate of 3% body weight per day (Verde and McCloskey, 1998; Welsh et al., 2009; Freeman et al., 2016). Contrary to carbon, nitrogen assimilation levels under both photosynthetic and non-photosynthetic conditions are low, suggesting alternative nitrogen sources are essential for life. Interestingly, nitrogen metabolism appears to be largely driven by non-photosynthetic microbes, highlighting the complexity of the *Cassiopea* holobiont (Freeman et al., 2016). Lipids are also translocated between host and symbiont (Mortillaro et al., 2009; Imbs, 2013; Imbs et al., 2014), but no cue has been found that explains the underlying mechanism or degree of translocation, although lipid composition and concentrations are known to shift under low light conditions in *Cassiopea* (Mortillaro et al., 2009). With the development of metabolomic tools and technologies such as NanoSIMS (nano-scale resolution chemical imaging mass spectrometry) (Kopp et al., 2013, 2015), *Cassiopea* offers an approachable and amenable system for the study of nutritional symbiosis. Given that this host can uptake multiple symbionts, future comparative studies conducted on

various colonization regimes and conditions will undoubtedly shed light on cnidarian-*Symbiodinium* symbiosis.

Similar to the topic of nutrient translocation, little is known about the plasticity in jellyfish nutrient cycling. Jellyfish planulae are all thought to be born symbiont-free, and then following settlement the sessile polyps acquire resources through ingestion of zooplankton. However, <10% of essential carbon is provided by heterotrophic means during the adult medusa stage, and decreased dependence on heterotrophy as a nitrogen source is seen with increasing medusa size (Kremer, 2005). In some coral species, a shift from photosynthesis to heterotrophy may be triggered by thermal stress; this trophic switching is believed to enhance host survival in the event of bleaching events (Rodrigues and Grottoli, 2007; Anthony et al., 2009). Under reduced light conditions, a short-term increase in levels of chlorophyll *a* was measured in *Cassiopea*, but no evidence of a shift toward heterotrophy was seen that might compensate for the perceived reduction in photosynthetic activity (Mortillaro et al., 2009). In a separate study, providing nutrient supplements to bleached *C. xamachana* did not prevent a reduction in medusa body mass (McGill and Pomory, 2008), pointing out the limitation of heterotrophic contributions to the overall energy budget.

## BEHAVIOR

### Fluid Dynamics

Jellyfish use bell contractions while swimming and changing direction in the water and to generate water currents that facilitate feeding and nutrient exchange. Both fluid dynamics and related biological relevance of these activated currents to *Cassiopea* medusae have been studied using empirical data and computational fluid dynamics (CFD) simulations (Hamlet et al., 2011; Santhanakrishnan et al., 2012). Although the pulsing behavior is cyclic (one cycle comprising a single bell contraction and expansion with pauses in between), it results in continuous flow along the substrate toward the medusa and continuous upward flow above the medusa. During contraction, vortices develop at the bell margins that are forced through the oral arms, where they are broken up. The frilly structure of the oral arms of *Cassiopea* ensures thorough mixing of the water over their surface and secondary mouths before it is pushed into an upward jet propulsion (Hamlet et al., 2011). Recently, a well-resolved three-dimensional CFD model of bell contraction in the upside-down jellyfish was developed to better ascertain the flows generated by these medusae (Hamlet et al., 2011; Hamlet and Miller, 2012; Santhanakrishnan et al., 2012). Implementation of these models presents the possibility of further investigations of the effect of jellyfish aggregations on the local fluid and nutrient dynamics of a habitat.

At the ecosystem level, the pulsing behavior of upside-down jellyfish affects nutrient release from the substrate. *Cassiopea*'s pulsing was shown to drive pore-water (interstitial water) up from the underlying sediment into the water column, allowing these derived nutrients to be used by the jellyfish and other reef organisms (Jantzen et al., 2010). This type of bioturbation (the disturbance of sediment by organisms) is an important mechanism that couples the nutrient-rich sediments with the

oligotrophic waters in which coral reefs occur. *Cassiopea* itself also releases organic matter, which is taken up by zooplankton in the water column (Niggli et al., 2010). Furthermore, studies have demonstrated that the presence of upside-down jellyfish can have an effect on local nutrient dynamics, greatly affecting local oxygen concentration and ammonium regeneration rates in space (between sediment patches with or without jellyfish) as well as in time (given the diurnal cycle of the photosynthetic symbionts; Welsh et al., 2009). These findings validate the notion that *Cassiopea* jellyfish play an important role in benthic-pelagic coupling of nutrient cycles, and some researchers even refer to the upside-down jellyfish as an ecosystem engineer (Jantzen et al., 2010). Further research is necessary to better understand the intricate role that *Cassiopea* medusae play in coastal ecosystems and nutrient cycling.

## Quiescence

Animal behavior is the product of numerous pathways, integrating both internal and external information to generate a global behavior. The internal state of an animal greatly affects its behavior—aroused animals act differently than those that are asleep. There is a debate as to how global brain states, like sleep, arise. It has been hypothesized that either specialized regions control the switch between wakefulness and sleep (a top-down mechanism), or neural networks have an emergent bias toward certain global states regulated by local circuits (a bottom-up mechanism). The fundamental question of the cellular mechanism controlling the sleep state is now approachable through detailed analysis of simple behavioral states.

Quiescence in the bilaterian model nematode *Caenorhabditis elegans* appears to be an emergent property; as the result of an internal network bias, it provides evidence against top-down regulation of a global brain state (Nichols et al., 2017). Unlike *C. elegans*, neurons in *Cassiopea*, and other cnidarians, are organized in non-centralized radially symmetrical nerve nets, and yet there exists deep conservation among cnidarian and bilaterian neural structure and neurotransmitters. Recently, a sleep-like state was identified in *Cassiopea*, making it the earliest diverging lineage (as a representative of Cnidaria) in which sleep has been observed (Nath et al., 2017). *Cassiopea* medusae display the three behavioral characteristics that define a sleep state: quiescence that is rapidly reversible, homeostatic regulation upon sleep deprivation, and a delayed response to sensory stimuli, called sensory depression. This recent recognition of a defined sleep-like state in *Cassiopea*, despite its lack of centralized nervous system, presents a unique opportunity to determine if sleep is, in fact, an emergent property of the earliest nerve networks. As an early diverging metazoan, *Cassiopea* is an important model for understanding scyphozoan behavior and the underlying evolutionary mechanisms that have arisen to control behavior in derived animal lineages.

## CASSIOPEA IN THE ENVIRONMENT

### Bioinvasion and Blooms

Molecular phylogenetic analyses demonstrated that some individuals of *Cassiopea* from the same geographic area fall into

different clades, evidencing cryptic species (Arai, 2001; Holland et al., 2004). At least two non-morphologically differentiated lineages of *Cassiopea* have been identified as alien species (Table 1). *Cassiopea* spp. have biological characteristics that make them potentially successful bioinvaders, such as their prolific asexual reproduction (Schiariti et al., 2014) and broad tolerance to variations in temperature and salinity (Morandini et al., 2017). The tenacity of *Cassiopea* spp. is demonstrated by their often well-established presence in disturbed or human-impacted habitats (Stoner et al., 2011). It is not surprising then, that species of *Cassiopea* have been documented as invasive in the Mediterranean (Galil et al., 1990; Çevik, 2006; Schembri et al., 2010; Bayha and Graham, 2014), Indo-Pacific (Papua New Guinea), Hawai'i (Holland et al., 2004), Australia (Keable and Ahyong, 2016), and Brazil (Morandini et al., 2017). Populations may occasionally reach enormous numbers (Stoner et al., 2011; Morandini et al., 2017) as a function of their environmental condition. With the frequency of these events potentially increasing according to studies on climate change (Richardson et al., 2009; Brotz et al., 2012), it necessitates development of methods for accurate taxonomic identification of cryptic species. These sudden proliferation events can be useful indicators of shifts in environmental conditions. Recent work has shown, to the contrary, that projected increased temperatures combined with increased exposure to UV-B radiation will lead to a general reduction in *Cassiopea* population size (Klein et al., 2016b). These findings are perplexing given the perception that jellyfish have an exceptional capacity to adapt to and thrive under conditions associated with ocean warming.

### Environmental Monitoring and Ecotoxicology

As marine systems worldwide continue to decline from local and global physical, chemical, and biological threats (De'ath et al., 2012; Epstein et al., 2016), the need to manage marine natural resources and reduce these threats is becoming increasingly more critical. Early detection and quantification tools are needed to assess risks that can have adverse impacts on the biological, physiological, and metabolic conditions at the level of the organism and the ecosystem (Markert et al., 2003; Downs, 2005). The use of jellyfish as biomonitors and/or bioindicators previously was not explored, possibly due to historical perceptions of their tolerance for poor environmental conditions and “boom or bust” population fluctuations. Biomonitors are used to derive both qualitative and quantitative information about the environment. There has been recent interest in establishing *Cassiopea* as a potential biomonitoring tool (i.e., indicator species) for enhancing water quality management. Previous studies have indicated jellyfish are able to accumulate trace metals in concentrations exceeding those present in ambient seawater, and concern exists that these could have potential for transfer up food webs (Romeo et al., 1987; Romeo and Gnassia-Barelli, 1992). For example, copper and zinc accumulate in *Cassiopea* (Templeman and Kingsford, 2010, 2012, 2015; Epstein et al., 2016) generally within hours to several days and with varying residence times (Fowler et al., 2004), while

phosphate concentrations in *C. xamachana* can reach an order of magnitude greater than those of ambient conditions, even when such levels are undetectable in seawater (Todd et al., 2006). The rapid response of *Cassiopea* medusae under exposure to metals and nutrients suggests they could serve as a useful indicator tool to detect and quantify short pulses of contaminants/pollutants entering a system, a role achieved by only a few of the current typical biomonitors.

In contrast to biomonitors, bioindicators are defined as organisms that will exhibit a change in structure or function that is linked to the biological effect of a contaminant at the organism, population, community, or ecosystem level (McCarty, 2002; McCarty and Munkittrick, 2008). Bioindicator species are used in laboratory bioassays to establish criteria for ecological sensitivity (e.g., LC<sub>50</sub>), but there is still a need to identify model organisms for standardization of these assays (Chapman, 1995; Edwards et al., 1996; Van Gestel and Van Brummelen, 1996). There is clear ecological relevance for exploring *Cassiopea* as a tool for ecotoxicological assessment—briefly defined as the study of effects of toxic chemicals (especially on the population level). As cnidarians, jellyfish occupy a key evolutionary position as early metazoans, serving important ecological roles as predators and prey (Faimali et al., 2014); additionally, they fuel pelagic food webs with dissolved and particulate organic matter (Niggel et al., 2010). *Cassiopea* offers an additional benefit as a bioindicator, as both the host jellyfish and dinoflagellate symbiont responses to environmental conditions can be assessed. Studies conducted on different life stages of *Cassiopea* exposed to copper or zinc demonstrated measurable effects at environmentally relevant concentrations (Templeman and Kingsford, 2015). In other studies, agricultural formulations of diuron and hexazinone at ecologically relevant concentrations caused measurable inhibition with respect to *Cassiopea* growth, photosynthetic efficiency, and symbiont density within 7 days of exposure (Rowen et al., 2017). A study looking at interactive responses between herbicides and salinity demonstrated that reduced salinity increased herbicide toxicity (Klein et al., 2016a). Pollutants in sewage and agro-chemicals have also been shown to cause reproductive and recruitment failure across most invertebrate phyla (Depledge and Billingham, 1999). There is an urgent need for new and improved bioassays to detect and assess new chemicals for their potential effects on marine invertebrates. *Cassiopea* has the potential to contribute extensively to understanding the effects of contaminants and pollutants on coastal marine ecosystems; the various genomic resources available for *Cassiopea* provide a tractable means to identify potential *in situ* molecular biomarkers and cellular diagnostic endpoints.

## OTHER LABORATORY APPLICATIONS

### Toxinology and Cnidome

Despite the ubiquity of cnidarian species in a variety of aquatic environments, toxinological research concerning cnidarian venom has been significantly delayed compared to advances seen in research applications related to venomous terrestrial animals (Turk and Kem, 2009). Early clinical research on cnidarian

venom validated a diversity of symptoms presented in human sting victims, including but not limited to anaphylaxis (Togias et al., 1985; Radwan and Burnett, 2001). Studies have also emphasized the potential for cnidarian bioactive proteins in pharmacological applications (Jha and Zi-Rong, 2004). *Cassiopea* medusae have a mild capacity to sting, and only a few cases of human envenomation have been reported to cause symptoms ranging from a rash, swelling, vomiting, and urticaria (Rifkin and Fenner, 1996). Cnidarian venom is delivered to prey and potential predators via the firing of microscopic nematocysts. In *C. andromeda*, five different types of nematocysts have been identified: a-isorhizas, O-isorhizas, euryteles, large oval birhopaloids, and small lemon-shaped birhopaloid (Heins et al., 2015). Studies including toxinological inferences have focused on several bioactive properties of crude venom extracts, which include cytolysis and hemolysis (Radwan and Burnett, 2001; Radwan et al., 2001, 2005; Torres et al., 2001). Neurotoxic effects were also identified in two of *Cassiopea*'s nematocyst types (birhopaloid and a-isorhiza) (Gülşahin, 2015). The ease at which *Cassiopea* can be collected globally in mangroves and cultured in the lab, provides a clear advantage to studying this species' venom, which has antitumor and antiprotozoal properties that may serve as future novel pharmacological and therapeutics agents (Orduña-Novoa et al., 2003; Morales-Landa et al., 2007; Mirshamsi et al., 2017). A recent study showed that *Cassiopea* crude venom induced apoptosis in human breast cancer tissue via reactive oxygen species (ROS) mediated cytotoxicity (Mirshamsi et al., 2017). *Cassiopea*, therefore, has potential for future bioactive natural product discovery through modern “venomics” approaches (genome, transcriptome, proteome, metabolome) that have applications to elucidating evolutionary mechanisms driving the complexity and diversity of cnidarian venom (Radwan et al., 2001; Casewell et al., 2013; Jouiaei et al., 2015).

### Cassiopea Virology

In comparison to bacterial components of the cnidarian holobiont, studies on the virome have received considerably less attention, but are of interest due to the potentially harmful effects that viruses can have on cnidarian health (Thurber and Correa, 2011; Correa et al., 2016). There is increasing recognition for biological and ecological importance of viruses in marine samples (Bosch et al., 2015; Thurber et al., 2017), and their role in evolution (Grasis et al., 2014). Preliminary data from the anthozoan *Exaiptasia*, has identified several RNA viruses, including those from *Partitiviridae* and *Picornaviridae* (Brüwer and Voolstra, 2017). The potential medical relevance, complex life strategies, as well as their host range and evolutionary history, the possible presence of RNA viruses associated with the jellyfish is of great interest to the field (Johnson, 2015; Koonin et al., 2015), and future studies should shed light on the yet-to-be explored evolutionary path of virus-cnidarian co-evolution. Furthermore, some cnidarians express genes that have been implicated as potential anti-retroviral agents (Ramessar et al., 2014), and our preliminary findings of several viruses in *Cassiopea* validate the necessity of these putative defense mechanisms. Going forward, studies on *Cassiopea* viromes may provide a unique opportunity to not only expand our understanding of the current host range

of Mononega- and retro-like viruses, but also to establish a reliable and robust model system for rigorous investigation of interactions within the holobiont as they relate to possible host immunity, in all stages of the jellyfish's life history.

## CASSIOPEA AS A LABORATORY RESOURCE

The ease at which the asexual polyp stage can be propagated in the laboratory using artificial seawater makes *Cassiopea* an attractive system for sustained culturing. Depending on the frequency of feeding, polyps are capable of developing motile planuloid buds within 24 h (Van Leishout and Martin, 1992). Swimming buds can settle onto a suitable substrate within 24 h and undergo metamorphosis into a polyp. Therefore, the continuous release of planuloid buds permits an aposymbiotic polyp to propagate a perpetual colony of asexual polyps. Currently, twelve *C. xamachana* lines (originally from Florida) have been established by the *Cassiopea* consortium. A draft *C. xamachana* genome has been assembled (ENA Accession: PRJEB23739), as well as transcriptomes of the aposymbiotic, symbiotic, and strobila stages (European Nucleotide Archive Accession: PRJEB21012). Future application of metabolomics approaches in *Cassiopea* research will also help generate a profile of the underlying metabolic pathways and metabolite dynamics that might be affected by environmental factors during key stages of *Cassiopea* development and symbiosis.

While aposymbiotic polyps can be propagated as described above, symbiotic polyps can be generated by providing the polyps with *Symbiodinium* spp. *Cassiopea* polyps are capable of forming associations with virtually all symbiotic *Symbiodinium* cultures (Thornhill et al., 2006; Lampert, 2016), making this an ideal system for comparative studies. The colonization characteristics of *Cassiopea* provide two tractable phenotypes to visually confirm variation in the symbiotic association. *Symbiodinium* density within the amoebocytes can vary depending on the colonizing species (Winstead et al., 2018), and strobilation timing also appears to vary accordingly (Lampert, 2016). Newly strobilated ephyrae are available for experimentation; likewise the adult medusae can also be acquired with relative ease, through animal transfer with public aquariums and through the recreational aquarium trade. In addition, only simple setups are required to rear each stage, making *Cassiopea* an easily manageable laboratory animal (Widmer, 2008). Fertilized eggs can be obtained from the brooding female adult medusae, confirmed by the initiation of initial cleavage post-collection (Smith, 1936; Gohar and Eisawy, 1960). *Cassiopea* are gonochoristic, with females identifiable through the presence of specialized central brood tentacles (Hofmann and Hadfield, 2002). Spawning can likely occur year-around under ideal conditions, and fertilized eggs collected directly from the brood tentacles after spawning (Gohar and Eisawy, 1960; Hummelinck, 1968). The planula larvae stage can also be acquired directly from the brooding female and used for additional experimentation. Tools for working with *Cassiopea* are increasingly being made available to researchers and educators, with many such protocols available online. In particular, a customized whole

mount *in situ* hybridization protocol has been developed for *Cassiopea*, along with other molecular tools and resources, which are accessible through the online portal (<http://sites.psu.edu/cassbase/>). Single cell injection for transgenic approaches is currently under development, with a promising outlook for becoming an important resource for mapping jellyfish molecular pathways.

## CONCLUSIONS

*Cassiopea* is a system predominantly studied for the many questions that can be addressed on interdependent organisms given its remarkable Cnidaria-*Symbiodinium* association. This review demonstrates that in addition to the effectiveness of the *Cassiopea* system for elucidating the complex processes underlying symbiosis, *Cassiopea* has potential to contribute substantially to our knowledge of a wide range of research topics within the field of invertebrate biology. The recent acquisition of genomics resources and development of several new molecular tools for *Cassiopea* sets this cnidarian apart as a model for identifying possible genotypic and phenotypic traits to support the hypothesis of co-evolution between *Cassiopea* and *Symbiodinium*. Given *Cassiopea*'s position as a well-established lab organism, the time is right for studies that seek to characterize possible changes in molecular composition (at the gene, metabolite or peptide-level) of one or both symbiotic organisms, phenotypic attributes that may have evolved as a result of this interspecific interaction, or the putative effects of ecological intimacy on each organism's level of adaptation to the shared environment. These questions, and countless others, can be properly interrogated by way of rigorous observations, diverse experimentation, and implementation of phylogenetic analyses in an attempt to infer potential reciprocal evolutionary change.

The *Cassiopea* system also has obvious applications to the fields of bacterial and viral co-evolution, from the dual perspective of understanding microbial symbiosis between either the cnidarian host or the associated dinoflagellate symbiont. Furthermore, *Cassiopea* shows promise as an effective bioindicator for our rapidly changing oceans, and as a biomonitor for further investigations of the medusa's potential impact on coastal ecology on a broader geographic scale. The relatively straight-forward culturing protocols and approachability of the system make *Cassiopea* particularly feasible as a teaching tool, not only at the college level but also from Kindergarten through grade 12. This review is a culmination of many years of multidisciplinary, collaborative research that has helped position the upside-down jellyfish *Cassiopea* as a valuable resource to researchers in the omics era seeking an effective model system to better understand the natural history and biodiversity of some of the earliest multicellular animals through studies on evolution, co-evolution and beyond.

## AUTHOR CONTRIBUTIONS

AO, MA, DB, LS-B, CF, EG-M, AJ-B, PL, ACMo, LM, LDM, ACMa, CN, SP, JS, SS, BS, MT, PT, MV, CW, JW, and MQM:

Provided written text for the sections within the manuscript; CA, AC, DH, TG, WF, and MM: provided expertise and edits to the manuscript.

## DEDICATION

We dedicate this manuscript to Robert Trench, who inspired many of us to begin working in Cassiopea.

## ACKNOWLEDGMENTS

We'd like to thank Todd LaJeunesse, Yixian Zheng, and Chen-Ming Fan for providing comments on the manuscript.

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