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PERSPECTIVE

Phaeodactylum tricornutum: An established model species for diatom molecular research and an emerging chassis for algal synthetic biology

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Abstract

Diatoms are prominent and highly diverse microalgae in aquatic environments. Compared with other diatom species, *Phaeodactylum tricornutum* is an "atypical diatom" displaying three different morphotypes and lacking the usual silica shell. Despite being of limited ecological relevance, its ease of growth in the laboratory and well-known physiology, alongside the steady increase in genome-enabled information coupled with effective tools for manipulating gene expression, have meant it has gained increased recognition as a powerful experimental model for molecular research on diatoms. We here present a brief overview of how over the last 25 years *P. tricornutum* has contributed to the unveiling of fundamental aspects of diatom biology, while also emerging as a new tool for algal process engineering and synthetic biology.

KEYWORDS
diatom, functional genomics, molecular model, *Phaeodactylum tricornutum*, synthetic biology

Abbreviations: 45582, Phatr3_J45582; 49202, Phatr3_J49202; 5-FOA, 5-fluoro-orotic acid; *Brs1*, blasticidin S-resistance gene; *CamV*, cauliflower mosaic virus 35S minimal promoter; *Cen6-Ars4-His3*, yeast maintenance region; CRISPR, clustered regularly interspaced short palindromic repeats; DPH, diatom phytochrome; FcpB and FcpF, fucoxanthine/chlorophyll binding protein B and F; GEM, genome-scale metabolic model; GFP, green fluorescent protein; GUS, β-glucuronidase; H4, histone H4; HDV, hepatitis delta virus ribozyme; HH, hammerhead ribozyme; HSF4.6a, heat shock factor 4.6a; LHCX1, light harvesting complex stress related protein 1; LOH, loss of heterozygosity; MoClo, modular cloning; NAT, nourseothricin *N*-acetyl transferase; NPQ, non-photochemical quenching; NR, nitrate reductase; Nub, NADH:ubiquinone oxidoreductase; *OriT*, origin of transfer; P2A, 2A self-cleaving peptide; Pbt, prohibitin; Pr, promoter sequences; *ShBleo*, *Streptoalloteichus hindustanus* bleomycin-resistance gene; SNV, single nucleotide variants; *Sp*Cas9, *Streptococcus pyogenes* Cas9; SVP, synaptobrevin/VAMP-like protein; TALEN, transcription activator-like effector nucleases; TE, transposable element; TF, transcription factor; Tr, terminator sequences; U6, small nuclear RNA of U6 small nuclear ribonucleoprotein; UGPase, UDP-glucose pyrophosphorylase; uLOOP, universal loop assembly; UMPS, uridine 5'-monophosphate synthase; YFP, yellow fluorescent protein.

INTRODUCTION

Diatoms are unicellular algae belonging to the division Heterokontophyta. The history of diatom research goes back more than 200 years, with microscopic studies revealing the magnificent structures of diatoms' silica cell walls (Kützing, 1834). Subsequent advances in ecology and oceanography established the critical role of these phototrophs in Earth's biogeochemical cycles (Field et al., 1998). Described by Bohlin in 1897, *Phaeodactylum tricornutum* was initially not classified as a diatom due to the absence of evident siliceous structures (Hendey et al., 1954) and its polymorphic morphotypes, a peculiarity not shared with other species (Barker, 1935; Lewin et al., 1958; Figure 1). Starting in the 1990s, however, and thanks to its easy cultivation coupled with reproducible genetic transformation and cryopreservation protocols, *Phaeodactylum* was regarded as a possible molecular model among the ~100,000 different diatom species (Malviya et al., 2016). Despite the initial reluctance of a part of the scientific community, which considered this "naked" diatom to be of limited ecological relevance as a poorly representative model, over the last two decades *P. tricornutum* has been a key player in unveiling the molecular secrets of diatoms, shedding light on physiological and metabolic peculiarities that can hardly be investigated in other diatom species. Moreover, these insights are leading to the establishment of new model species that can answer specific questions pertaining to the ecology or life cycles of diatoms, which cannot be addressed in *P. tricornutum*.

THE MOLECULAR TOOLBOX FOR *PHAEODACTYLUM TRICORNUTUM*

The first genetic transformations of *Phaeodactylum tricornutum* were achieved by microparticle bombardment by Apt et al. (1996) and Falciatore et al. (1999), shortly after those of the diatoms *Cyclotella cryptica* and *Navicula saprophila* (Dunahay et al., 1995). Transformation appears to be more reproducible and efficient in *P. tricornutum* than the other diatoms, likely because its cell wall is only partially silicified and does not have an absolute requirement of silicate. Moreover, the ability to efficiently grow *P. tricornutum* axenically and to recover independent colonies on agar plates following transformation and appropriated selection have facilitated the molecular characterization of transgenic lines compared to other diatoms. Genetic studies have been initiated in *P. tricornutum* thanks to the development of a variety of molecular tools, including selectable antibiotic resistance genes, reporter genes, recombination cloning tools for protein tagging and over-expression, and a variety of promoters and terminators to drive gene expression (Falciatore et al., 2020). Because of this progress, a large community of scientists joined efforts to sequence and annotate the *P. tricornutum* nuclear (27.4 Mbp), plastid (117 kbp), and mitochondrial (77.3 kbp) genomes (Pt1 ecotype CCAP1055/1, also named Pt1 8.6/CCMP2561/CCMP632; Bowler et al., 2008; Figure 1). The comparative analysis of the *P. tricornutum* genome with that of the centric species *Thalassiosira pseudonana*

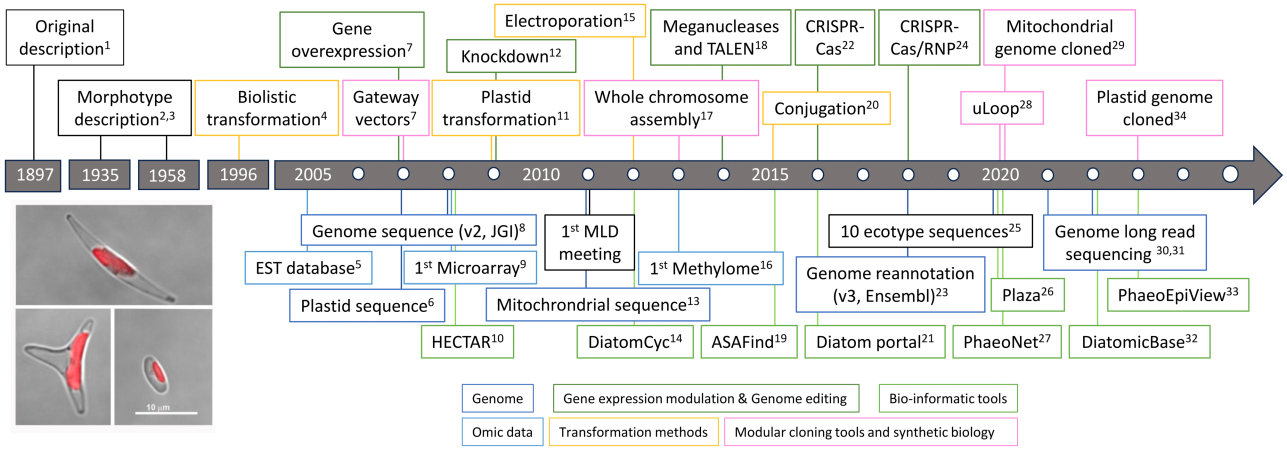

FIGURE 1 Milestones in the *Phaeodactylum tricornutum* molecular research. [1]von Bohlin (1897), [2]Barker (1935), [3]Lewin et al. (1958), [4]Apt et al. (1996), [5]Maheswari et al. (2005), [6]Oudot-Le Secq et al. (2007), [7]Siaut et al. (2007), [8]Bowler et al. (2008), [9]Allen et al. (2008), [10]Gschloessl et al. (2008; http://www.sb-roscoff.fr/hectar/), [11]Materna et al. (2009), [12]De Riso et al. (2009), [13]Oudot-Le Secq and Green (2011), [14]Fabris et al. (2012; http://www.diatomcyc.org), [15]Niu et al. (2012), [16]Veluchamy et al. (2013), [17]Karas et al. (2013), [18]Daboussi et al. (2014), [19]Gruber et al. (2015), [20]Karas et al. (2015), [21]Ashworth et al. (2016; http://networks.systemsbiology.net/diatom-portal/); [22]Nymark et al. (2016), [23]Rastogi et al. (2018), [24]Serif et al. (2018), [25]Rastogi et al. (2020), [26]Osuna-Cruz et al. (2020; https://bioinformatics.psb.ugent.be/plaza/versions/plaza_diatoms_01/); [27]Ait-Mohamed et al. (2020), [28]Pollak et al. (2020), [29]Cochrane et al. (2020), [30] Filloramo et al. (2021), [31]Giguere et al. (2022, [32]https://www.diatomicsbase.bio.ens.psl.eu/; [33]Wu et al. (2023), [34]Walker et al. (2023). MLD, Molecular Life of Diatoms. The figure also shows confocal microscopy images of *P. tricornutum* morphotypes (fusiform, triradiate, and oval) that were taken merging the bright-field and chlorophyll *a* autofluorescence channels. In red, *P. tricornutum* plastid. [Color figure can be viewed at wileyonlinelibrary.com]

published 2 years earlier (Armbrust et al., 2004), and subsequently with other diatoms, highlighted a peculiar gene repertoire, including, in the ~12,000 *P. tricornutum* predicted genes, almost an equivalent number of animal-like and plant-like genes, a large fraction of core diatom specific (16%) and of species-specific (26%) genes, genes of bacterial origin (4.1%; Rastogi et al., 2018), and strong molecular divergences due to rapid rate of diversification (Mock et al., 2022).

Strategies aimed at perturbing gene expression through both overexpression and gene silencing enabled the first characterization of diatom gene products by reverse genetics (Figure 1). In the 2000s, the advent of genome editing launched a new era for diatom molecular research. Starting with meganucleases and TALENs (Daboussi et al., 2014) and followed by the CRISPR/Cas system (Nymark et al., 2016), rapidly evolving technologies now allow us to study diatom gene function efficiently, accurately and cost-effectively (Figures 1 and 2). The recent development of a new and efficient transformation method using bacterial conjugation represents an additional milestone in diatom research. This achievement was enabled by the creation of the first nuclear episomal plasmid for diatoms, known as p0521s (Karas et al., 2015), that can be transferred via conjugation. Genetic elements of p0521s include regions of yeast (YAC) and bacterial (BAC) artificial chromosomes, a small region of *Phaeodactylum tricornutum* DNA, and an antibiotic marker to ensure episome selection and maintenance in diatoms. Notably, the presence of low G+C DNA regions within the YAC has been shown to facilitate the efficient replication of p0521s (Diner et al., 2016; Karas et al., 2015). Furthermore, studies have revealed that various DNA fragments with a G+C content of less than approximately 33% and a sequence length exceeding 500 base pairs can act like putative centromeres, supporting episomal replication (Diner et al., 2017).

Diatom functional genomics is also benefiting from the increase in both -omic data generated in *Phaeodactylum tricornutum*, wild-type and mutant strains, and tools for analyses (Figure 1). To share and optimally exploit resources generated by different laboratories, a recent effort aims to centralize these data into a single database, DiatOmicBase. This already public resource is also linked to other tools for comparative genomics (Plaza) or analysis of transcriptional and metabolic networks (DiatomCyc, DiatomPortal, and PhaeoNet) and offers a transcriptomic module enabling the analysis of either published or personally generated RNA-Seq datasets.

INSIGHT INTO THE BIOLOGY OF DIATOMS

Over the last two decades, *Phaeodactylum tricornutum* research has vastly improved our understanding of diatom biology (for a recent overview see Falciatore & Mock, 2022). While an exhaustive summary of these discoveries is beyond the scope of this review, in this section we highlight some of the studies that we consider indicative of how the resources developed via this species can be exploited to answer a wide range of biological questions.

As diatoms are major photosynthetic actors in the oceans, many efforts have been devoted to the study of the regulation of photosynthesis. First, gene knockdown helped identify the key role of a member of the light-harvesting complex stress-related protein family, LHCX1, in the regulation of the exceptional photoprotection capacity of diatoms (Bailleul et al., 2010). The analysis of several *Phaeodactylum tricornutum* natural variants showing different *lhcx*1 expression levels, as well as different NPQ levels, revealed that this protein was the target of adaptive evolution and could modulate natural photoresponse variability. The more recent generation of *lhcx*1 knock-out mutants contributed to the further characterization of this process. The finding that the complementation of a *lhcx*1 mutant with LHCX1 variants harboring targeted mutations in putative protonatable residues (Buck et al., 2021; Giovagnetti et al., 2022) did not alter NPQ provided evidence that LHCX1 is not involved in lumenal pH sensing, unlike its plant or green algal orthologs. Complementation of *lhcx*1 has also been instrumental for determining the functional redundancy of some, but not all, of the expanded LHCX family members (Buck et al., 2019). Additional information has been derived by the reconstructed three-dimensional structure of the *P. tricornutum* plastid. These studies revealed that while there is no clear distinction between grana and stroma lamellae (as opposed to thylakoids of green algae), there is a topological segregation of PSI and PSII in different domains, which could play a role in preventing the loss of efficiency of photosynthetic system (Flori et al., 2017). Finally, integrated biophysical characterizations of photosynthetic processes and targeted mutagenesis of the mitochondrial activity unveiled a strong energetic coupling between plastids and mitochondria, contributing to efficient diatom CO_2 assimilation (Bailleul et al., 2015).

Genome-enabled exploration of *Phaeodactylum tricorutum* has also revealed important features of diatom nutrient metabolism (Coale et al., 2022; Kroth & Matsuda, 2022; Smith & Allen, 2022). Examples include the discovery of a functional urea cycle involved in the metabolism optimization under nitrogen limitation (Allen et al., 2011), or the role of the nitrate reductase in controlling the balance between nitrate transport and assimilation, and the distribution of carbon flux (Levitan et al., 2015; McCarthy et al., 2017). A recent study also evidenced a coordinated regulation of phosphorus and nitrogen metabolism mediated by sophisticated sensing and signaling

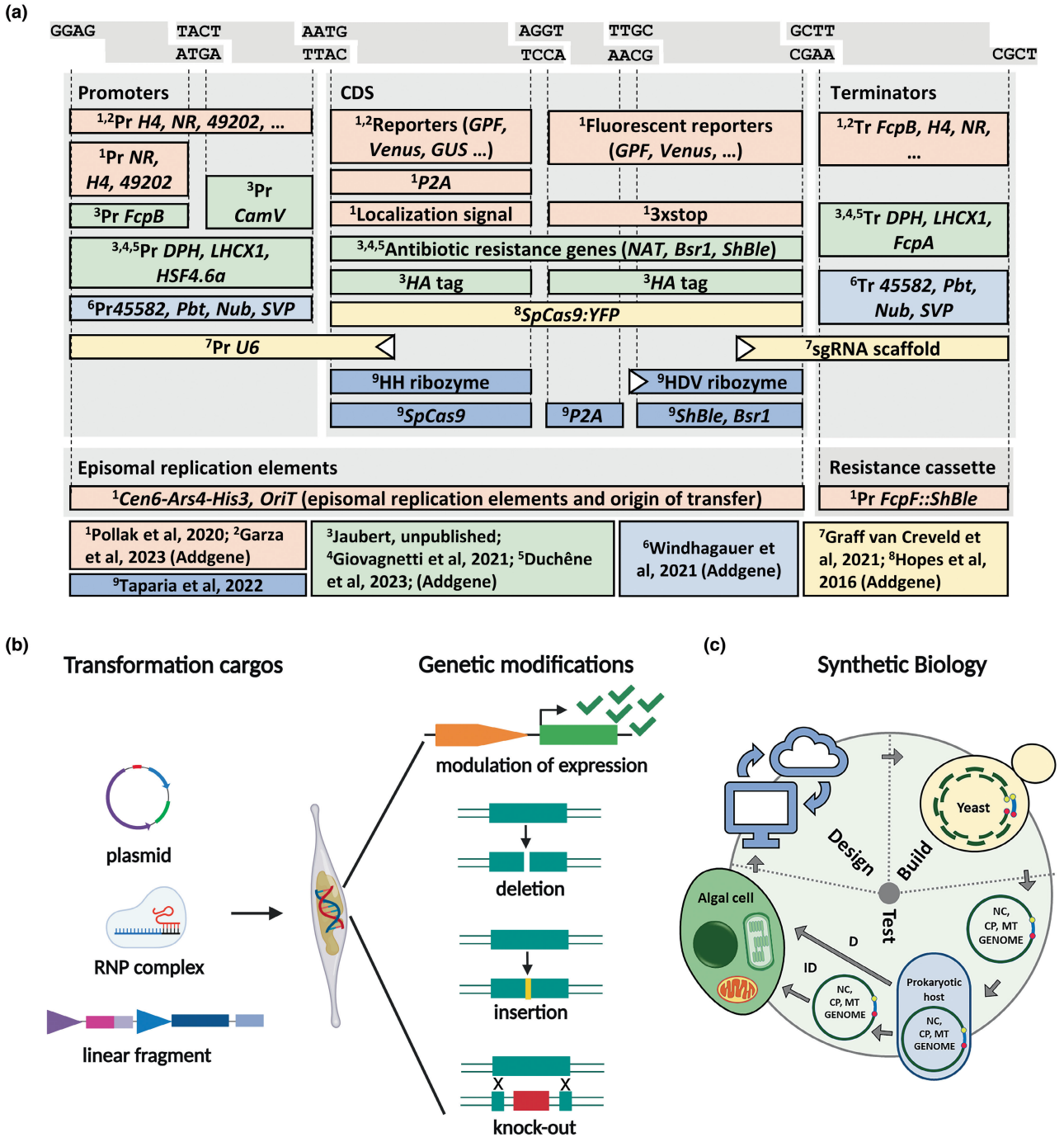

FIGURE 2 Tools for genetic engineering and synthetic biology in *Phaeodactylum tricornutum*. (a) Overview of the *P. tricornutum* basic parts (level 0) library available for MoClo following the MoClo syntax. The color code refers to the different laboratories that have generated the blocks. Vectors deposited on Addgene are indicated. (b) Graphic representation of the strategies used to obtain engineered strains by targeted genetic modification. The scheme illustrates different transformation cargos that can be delivered and examples of genetic modifications that can be obtained in *P. tricornutum* (created with Biorender.com). (c) The design–build–test cycle for engineering *P. tricornutum* genomes, modified from Cochrane et al. (2020). Designed synthetic genomes: nuclear (NC), mitochondrial (MT), and chloroplast (CP) will be built in yeast and then transferred to a prokaryotic host to be delivered directly (D), for example, via conjugation, or indirectly (ID), for example, via electroporation, to the appropriate cell compartment to test for designed functions. [Color figure can be viewed at wileyonlinelibrary.com]

cascades involving calcium as a second messenger (Helliwell et al., 2021). It is also worth mentioning that the first transcriptomic studies performed in *P. tricornutum* cells under iron-limited conditions led to the identification of novel regulators of the iron response, such as the iron starvation-induced proteins (ISIPs; Allen et al., 2008). Following later functional studies (Coale et al., 2022), ISIPs are now widely used to

predict the response to nutrient availability in environmental studies (Nef et al., 2022).

The recent discovery of the diatom circadian clock is another good example of how research on *Phaedactylum tricornutum* is contributing to the discovery of regulators of critical biological processes. Although diatoms exhibit diel rhythms in many fundamental processes (Häfker et al., 2023), the existence of an endogenous clock controlling these rhythms has long been a matter of debate because there are no clear orthologs of the bacteria, fungi, animals, or plants circadian clock components in the diatom genomes. The search for the diatom clock began on the basis of a robust working hypothesis: As in other eukaryotes, the diatom clock must involve TFs with strong diurnal rhythmic expression embedded in autoregulatory feedback loops. The first diatom timekeeper component was indeed identified by searching *P. tricornutum* TFs with strong rhythmic expression and by assessing the effect of ectopic expression on circadian regulation (Annunziata et al., 2019). Named RITMO1, this key player of the circadian clock is highly conserved in all diatoms. Other clock components are currently being identified using RITMO1 as the entry point in genome-wide DNA–protein and protein–protein assays.

Phaeodactylum tricornutum is also helping us to understand diatom genome structure and evolution, thanks to the improved genomic resources and information about genetic and epigenetic mechanisms controlling gene expression (Zhao et al., 2022). Moreover, as a powerful genetic model, *P. tricornutum* is allowing researchers to clarify the mechanisms underlying the extensive intraspecific variability (at the level of SNV) observed within diatom populations by metagenomic analysis. The hypothesis that mitotic interhomolog recombination may play an important role in generating diversity was first hypothesized by using next-generation sequencing to map and quantify the genomic changes arising within clonally propagated *Seminavis robusta* and *P. tricornutum* cell cultures (Bulankova et al., 2021). These analyses indicated a significant accumulation of novel haplotypes from single cells, which, in the absence of sex, could result from the genetic exchange between the haplotypes from the same individuals, potentially leading to copy number variation and copy-neutral LOH. Support for this hypothesis derives from an elegant readout system based on the use of *P. tricornutum* strains containing two different mutant alleles of the *PtUMPS*, an ideal counter-selectable marker gene because its disruption induces both tolerance to 5-FOA and uracil auxotrophy. By cultivating *ptumps*−/− lines, first in non-selective conditions to permit possible restoration of wild-type alleles and then in media with no uracil and toxic 5-FOA, it has been possible to monitor and quantify interhomolog recombinations leading to the restoration of *PtUMPS*. It has been proposed that these events, which increase under stress, could represent an evolutionary benefit for diatoms in the environment, especially during clonal competition (Bulankova et al., 2021).

TOWARDS DIATOM SYNTHETIC BIOLOGY

An expanding molecular toolkit (Figures 1 and 2), along with computational approaches for generating genome-scale metabolic models (GEMs; e.g., Broddrick et al., 2019), make *Phaeodactylum tricornutum* a promising algal system for metabolic engineering. Several *P. tricornutum* strains showing novel traits have been already generated, including auxotrophic variants (Slattery et al., 2020) that decrease propagation costs and enhance suitability for industrial manufacturing (Slattery et al., 2022), strains with an increased production of triacylglycerol following the disruption of the endogenous *UGPase* (Daboussi et al., 2014), and strains producing natural plant products (triterpenoids or monoterpenoid geraniol) via the heterologous expression of plant genes (D'Adamo et al., 2019; Fabris et al., 2020).

Cloning steps of multigene constructs are accelerated and potentiated thanks to standardized synthetic biology tools and workflows, such as the MoClo (Werner et al., 2012). By using type IIS restriction enzymes, such systems enable the assembly of different genetic elements in predefined arrangements and the successive custom combination of multiple transcriptional units in a single vector, ready to be delivered into the cell. A library of basic genetic elements for *Phaeodactylum tricornutum* (Figure 2a) for use in MoClo systems such as uLoop and Golden Gate has been initiated by different laboratories. Following the widely used standards syntax (Patron et al., 2015), non-species-specific basic modules can be shared between communities, extending the possibility of synthetic plasmid buildings.

The production of algal designer strains often requires the introduction of multiple genetic modifications. Compared to the more limited capacity of CRISPR to generate multiple modifications, whole chromosome replacement offers virtually limitless possibilities in genome engineering. This methodology is inspired by groundbreaking technologies developed for the engineering of synthetic mycoplasma (Gibson et al., 2010), *Escherichia coli* (Fredens et al., 2019), and yeast (Annaluru et al., 2014). The process entails the construction of DNA within host organisms such as *E. coli* and/or yeast, followed by its reintroduction into the target organism. Recently, such effort has been proposed for *Phaeodactylum tricornutum* (Pampuch et al., 2022), with the aim to synthesize the entire genome as fifty ~500 kbp chromosomes to facilitate the assembly process and increase the chances of intact delivery of synthetic

chromosomes. This proposed design includes multiple modifications such as the removal of non-essential genes, elimination of synonymous codons, or humanizing of algal genes that would have genes replaced with their human orthologs to mimic human post-translational modifications (Pampuch et al., 2022). So far, researchers have successfully assembled two nuclear chromosomes as well as mitochondrial and chloroplast genomes (Figures 1 and 2c) in yeast and demonstrated that they can replicate in *E. coli*. The next task is to optimize compartment-specific selection markers and initiate testing of the delivery methods of these chromosomes. One potential avenue being explored is conjugation, which has demonstrated the capability to deliver and stably propagate DNA fragments of at least 49 kb in *P. tricornutum* (Karas et al., 2015). The upper limits of this delivery method to algal cells are still subject to empirical verification. The establishment of strains compatible with the faithful propagation of synthetic chromosomes may require additional engineering such as the generation of recombination-deficient strains, as described in Pampuch et al. (2022). Once these prerequisites have been established, creating and installing synthetic versions of current chromosomes or creating neo-chromosomes with desired new functions should be possible. The near-term goals to create synthetic genomes are to: (1) explore the most advantageous replication mode for synthetic nuclear chromosomes, such as linear versus circular configurations, (2) establish random mutagenesis method to find out which genes are essential, (3) optimize seamless gene deletion methods, (4) install landing pads, and (5) complete synthesis of the smallest chromosome (chr. 25; Giguere et al., 2022).

CONCLUSIONS

Phaeodactylum tricornutum has proven highly successful in revealing fundamental aspects of diatom biology that are relevant to many species. Diatom research is now greatly benefitting from the establishment of new ecologically relevant model systems (Ferrante et al., 2023; Otte et al., 2023; Poulsen & Kröger, 2023). Without doubt, the fundamental and practical insights gained and still to come through the study of *P. tricornutum* will support comparative investigations, essential for addressing the significance of diatom diversity in the context of adaptation and evolution. The substantial ability for genetic engineering in *P. tricornutum*, coupled with recent advances in synthetic biology, will empower studies testing the effects of gene/pathway variants on physiology and metabolism or seeking to generate new desirable traits using endogenous gene variants, heterologous genes, or a combination of both.

The wide uses of *Phaeodactylum tricornutum* would justify efforts to generate public collections of mutants, as has previously been done for other photosynthetic model organisms of the green lineage, for example, Chlamydomonas or Arabidopsis. Such a resource would enable many laboratories to systematically study a broad range of fundamental processes and define functions for the numerous genes still defined as "diatom specific" or as "unknown." The diatom molecular community now has the expertise to develop this ambitious project. Beyond *P. tricornutum*, it becomes increasingly important to reach a consensus on the most appropriate diatom model species on which to focus similar efforts.

AUTHOR CONTRIBUTIONS

Monia T. Russo: Conceptualization (equal); writing – original draft (equal). **Alessandra Rogato:** Conceptualization (equal); writing – original draft (equal). **Marianne Jaubert:** Conceptualization (equal); writing – original draft (equal). **Bogumil J. Karas:** Conceptualization (equal); writing – original draft (equal). **Angela Falciatore:** Conceptualization (equal); writing – original draft (equal).

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