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PERSPECTIVE

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Biocatalyst discovery and design for plastics deconstruction: A multi-scale perspective

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Abstract

Plastic waste accumulation poses significant environmental challenges due to a lack of economical solutions for the molecular deconstruction of diverse synthetic polymers. Biological-based degradation offers promise but is hindered by the crystallinity, hydrophobicity, and additive complexity of plastics, which restrict biocatalyst access and activity. To address these barriers, we propose a multi-scale framework that combines detailed materials characterization, optimization of plastic-biomolecular interfacial interactions, and enhancement of biocatalytic kinetics to develop effective plastic-deconstructing enzymes. This approach leverages principles from reaction kinetics, transport and interfacial phenomena, and enzyme engineering to systematically address barriers across diverse plastic types. Our framework aims to accelerate the discovery and optimization of biocatalysts capable of scalable, selective, and efficient deconstruction of plastic waste. These advances hold potential to enable sustainable biological recycling and upcycling pathways, contributing to global efforts in mitigating plastic pollution and promoting circular material economies.

KEYWORDS
biocatalytic kinetics, biodeconstruction, interfacial phenomena, plastic waste, polymer characterization

1 | INTRODUCTION

Plastic waste continues to accumulate globally, posing significant environmental, health, and economic challenges.[1,2] Despite growing awareness, recycling and reuse of plastics remain limited; mechanical recycling, the most common method, often yields materials with reduced performance and value.[3] Thus, there is a growing need for strategies that deconstruct polymers and upcycle these products into new materials and chemicals. Chemical processes designed to deconstruct plastics have yet to become economically feasible in part due to intense operating conditions and the quality of the resulting products.[4,5] Enzymatic deconstruction of amorphous, hydrolyzable plastics such as polyethylene terephthalate (PET) has emerged as an industrially viable alternative to energy-intensive chemical recycling processes.[6,7] However, biological approaches for other major plastic types remain underdeveloped. This is largely due to the inherent complexity of these plastic materials, including variability in molecular weight, crystallinity, and hydrophobicity, along with a need for chemistries rarely seen in biology, which present unique challenges for biocatalyst design.[8] To address these challenges, we propose a multi-scale framework based on chemical engineering principles from reaction kinetics, transport and interfacial phenomena, and materials characterization to guide enzyme discovery and optimization for plastics deconstruction.

Effective biocatalysts, those with strong substrate recognition, high catalytic turnover, and robust stability, are central to any biological strategy for plastics deconstruction. However, the current list of plastic-active biocatalysts and microbes is limited[9] in both reaction rates and the diversity of plastics types and formats they can address.

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Expanding this toolkit requires sustained discovery efforts, including meta-omics analyses (e.g., DNA, RNA, and protein profiling) and data mining of large variant libraries using established and emerging AI/ML strategies for candidate identification, along with rigorous biochemical characterization.[10–14] However, optimization for industrial scale deployment cannot rely solely on empirical screening. A chemical engineering perspective provides a mechanistic foundation for rational design by linking polymer properties (e.g., hydrophobicity, crystallinity, chain length) with biocatalyst features (e.g., surface charge, binding domains, active-site geometry) that govern deconstruction. Within this framework, two key engineering bottlenecks to plastics biodeconstruction become readily apparent: (1) transport and interfacial phenomena between hydrophobic plastics and hydrophilic enzymes that limit substrate binding interactions; and (2) catalytic mechanisms capable of accommodating long, variable polymer chains to enable high processivity and efficient degradation.

The challenges encountered in enzymatic plastics deconstruction are not unique; similar barriers arise in the biodegradation of plant biomass, which also features large, insoluble, crystalline substrates.[15–19] This parallel offers a useful case study for informing strategies in plastics biocatalysis. First, precise material definition, such as quantifying surface accessibility, was essential for interpreting hydrolytic performance, and led to the recognition of distinct enzymatic mechanisms when processing amorphous or crystalline domains.[20–22] Second, improving weak enzyme-substrate association required fusion of substrate binding domains, such as cellulose-binding carbohydrate-binding modules (CBMs), to catalytic hydrolases.[23,24] Third, lignin cleavage was accelerated by pairing lytic polysaccharide monooxygenases (LPMOs), which create multiple functionalized sites for chain scission and reduce polymer crystallinity, with hydrolases that then cleave the exposed chain.[25,26] Collectively, these lignocellulolytic strategies offer a blueprint for designing biocatalysts capable of overcoming the structural and chemical complexity of synthetic polymers.

In this perspective, we propose an integrated multi-scale framework to guide the identification and engineering of biological systems capable of deconstructing the highly heterogeneous stream of post-consumer plastics waste (Figure 1). This framework begins with thorough appreciation and characterization of key material properties, such as additive content, crystallinity, and molecular weight, that define the physical and chemical boundaries for enzymatic activity. Once a polymer template is selected, both abiotic (i.e., environmental) and biotic (i.e., enzyme or cell) factors must be considered to understand and optimize the interfacial phenomena that governs biocatalyst-substrate binding. We review both rational and empirical strategies for improving the catalytic potential of plastic degrading enzymes. The discovery, design, and optimization of such biocatalysts requires an integration of material properties, interfacial science, and kinetics to ensure broad applicability across diverse plastics wastes.

2 | MATERIAL PROPERTIES SET THE LIMITS FOR BIODECONSTRUCTION SYSTEMS

Plastic deconstruction rates are highly sensitive to material characteristics and properties,[27–31] meaning that any discussion of biological deconstruction must be qualified by a definition of the material used.

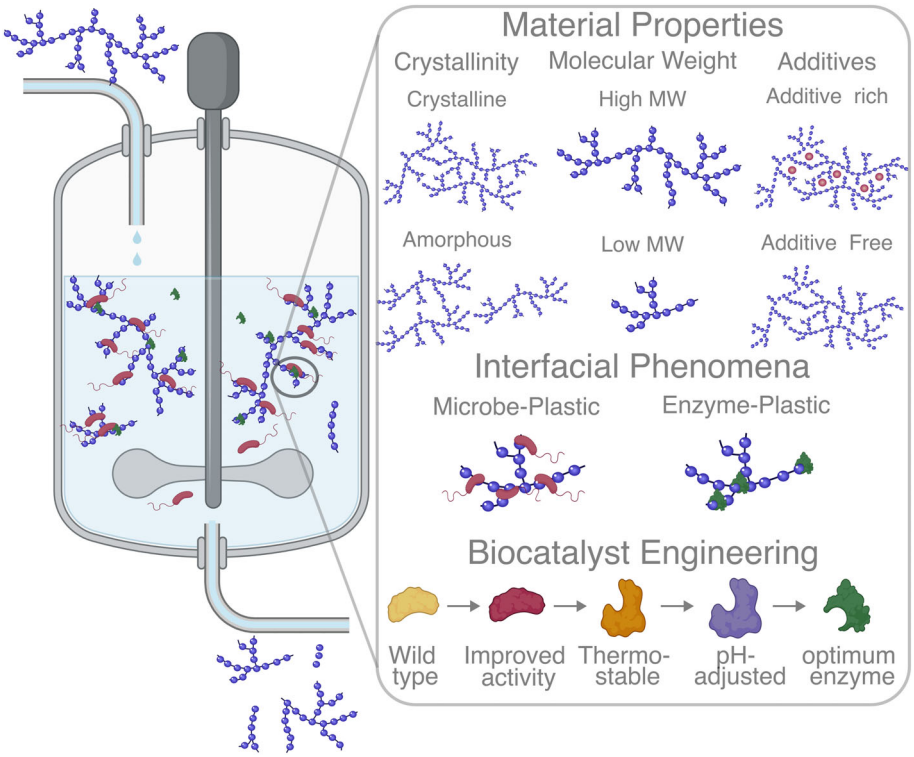

FIGURE 1 Biological plastics deconstruction must be approached systemically with a chemical engineering lens to enable substantive progress. Material properties, interfacial phenomena, and the discovery and engineering of biocatalysts should be evaluated independently and with appropriately chosen substrates to guide development of plastics biodeconstruction efforts.

Plastics are complex composites consisting of more than just polymer chains. They often include additive packages (including slip agents, antioxidants, plasticizers, and colorants) and may be processed into co-polymers or multi-layer formats.[32] Even within the same resin code, plastics can vary significantly in mechanical properties such as elastic modulus, ductility, and rigidity due to differences in manufacturing processes.[33] These mechanical properties are governed by polymer chain architecture, namely the crystallinity and branching of the polymer chains,[34,35] the molecular weight, and the presence of additives. Importantly, enzymatic access to polymer chains is constrained by crystallinity[36] and molecular weight, defining regimes within which biodeconstruction becomes possible. Processing-dependent effects (e.g. extrusion or molding) can influence secondary morphological features such as crystallinity heterogeneity, chain orientation, and geometry, which impact degradability. However, these processing-dependent properties are reversible and can be mitigated through thermal, chemical, or mechanical pretreatment,[37,38] reducing their impact compared to intrinsic properties like molecular weight or chemical structure (Table 1).[39] Thus, three key properties of the plastic—additive content, crystallinity, and molecular weight—must be defined for each plastic to assess its biodegradability.

Additive effects on deconstruction vary by plastic type and must be understood in context. For non-hydrolyzable plastics, antioxidants inhibit oxidative (bio)chemistries required for chain scission.[40] For example, removing additives from HDPE led to a 4.3-fold increase in product yield during chemical deconstruction over a $Pt/WO_3/ZrO_2$ catalyst.[41] Conversely, hydrolyzable plastics do not rely on oxidative pathways[40] and are less affected by antioxidants. Slip agents added to reduce friction and improve surface smoothness are chemically similar to base polymers and susceptible to enzymatic oxidation and hydrolysis.[42–45] Plastic-active enzymes may preferentially target these smaller, linear additives due to better active-site binding.[46,47] This can divert enzymatic activity away from the polymer backbone, reduce the sensitivity of degradation assays, and confound results with non-polymer degradation products.

To accurately evaluate the biodeconstruction potential of plastics and identify enzyme candidates with verified backbone degradation, additives and polymers should be separated and studied independently. Extraction methods such as ultrasonic, shake-flask, Soxhlet, or microwave assisted extraction[48] can isolate additives, yielding pure polymer to use in biodeconstruction studies. Additive mixtures can be analyzed via liquid chromatography MS (LC–MS), and individual compounds purified or purchased for targeted biodegradation studies. Once each component is characterized, cross-compatibility of degradation conditions for both the additive and polymer components in the plastic can be assessed, and the enzyme engineered to increase robustness with more real-world materials. For instance, enzymes optimized for polymer deconstruction may not tolerate solvents or pH conditions required for additive breakdown. These interactions determine whether a particular plastic can be deconstructed in a one-pot reaction, or if additive pre-treatment is necessary. We strongly recommend using purified polymers and additives for independent validation of biodegradation prior to testing post-consumer materials. This approach minimizes false negatives caused by additive interference and ensures accurate assessment of enzymatic activity. If single-pot enzymatic deconstruction is not possible, particularly in cases where inhibitory additives like antioxidants are present in polyolefins, pre-separation becomes essential. Isolating the polymer allows subsequent processing steps to focus on pure polymer chains, enabling the use of standardized enzymatic treatments across resin codes. This strategy is analogous to crude oil refining, where distillation separates components for targeted downstream processing.[49]

Independent of additives, plastics within a resin code share backbone chemistry but differ in physical structure due to variations in chain architecture.[34,35,50,51] Branching density, branch length, and molecular weight drive chain packing and subsequently crystallinity, which in turn affect enzyme accessibility.[50,51] Lower crystallinity increases surface area for enzyme binding, facilitating deconstruction.[36,50] This has been well-documented in PET biodeconstruction, where PET hydrolases are only active on polymers with <15–23% crystallinity.[13,36] Crystallinity thresholds for non-PET plastics remain undefined due to limited enzymatic systems.[40] To address this, plastics of varying crystallinity should be assessed on microbial and enzymatic systems. Plastics of varying crystallinity can be generated during synthesis by altering polymerization temperatures and pressures[52] or post-synthesis via solvent extractions or nitric acid etching on existing polymers.[53] Amorphization techniques, such as alkali pre-treatment, can also be used to decrease crystallinity prior to enzymatic processing.[54] Alternatively, enzymes can be engineered for improved

TABLE 1 Effects of pretreating plastics and impacts on biological accessibility.[37,38]

Pretreatment type	Techniques/processes	Polymer modification	Bio-accessibility
Mechanical	Grinding, milling, high-shear, size reduction	Increases surface area, exposes internal polymer	Increase in number of binding sites
Thermal	Heat treatment, hydrothermal processes	Increases chain mobility, can cause chain scission	More frequent binding and catalysis of polymer chains
Chemical/ Oxidative	Acid/alkali hydrolysis, chemical oxidants, UV, photooxidation	Generates polar surface functional groups, radical sites	Improved adhesion/ colonization of the plastic surface
Non-thermal physical	Plasma, ultrasound, microwave	Alters surface chemistry and surface structure	Improved adhesion/ colonization of the plastic surface

thermostability above the polymer glass transition temperature (T_g), where chain mobility enhances enzyme binding. For example, PET hydrolases have been engineered to operate at 80°C (PET $T_g \approx 75$°C), enabling hydrolysis of PET with up to 39% crystallinity.[55] Although non-hydrolyzable plastics such as LDPE already exist well above their glass transition temperature under physiological conditions (LDPE Tg ≈ −100°C),[56] engineering enzymes with increased thermostability can further enhance polymer chain mobility and improve bioaccessibility of these substrates.[57] However, enzyme engineering for improved thermostability is limited for plastics with a T_g above the 40–90°C range. Otherwise, the discovery or de novo design of small enzymes capable of penetrating crystalline domains may be required.

Low molecular weight plastics are theoretically more amenable to biodeconstruction due to their shorter chain lengths, which require fewer bond-cleavage events. However, shorter chains exhibit reduced polymer entanglement[58,59] and more chain mobility relative to higher molecular weight polymers, which typically promotes more efficient packing and increased crystallinity.[60] This relationship between polymer molecular weight and crystallinity is non-linear as it is impacted by several factors such as chain branching, processing conditions, and monomer identity.[61,62] Therefore, to delineate the activity range of biological systems, plastics of varying molecular weights should be systematically tested. Such plastics can be synthesized by changing reaction conditions to control molecular weight.[63] Given the added complexity of engineering enzymes or introducing pre-processing steps for high molecular weight and high crystallinity plastics with inherently unfavorable properties for biocatalyst binding and function, initial testing should prioritize low molecular weight substrates that have low crystallinity. These serve as baseline materials to establish enzymatic activity, with subsequent testing on more recalcitrant plastics used to define the upper bounds of biodeconstruction. It is important to note that low molecular weight polymers must still fall within the representative molecular weight distribution of the plastic class under investigation. For example, a polyethylene with a molecular weight of 1000 g/mol is not an appropriate substrate, as it falls well below the minimum for characteristic polymer entanglement of ∼4200 g/mol and the typical range of ∼10,000 to 100,000 g/mol of typical polyethylenes.[52]

3 | INTERFACIAL PHENOMENA INITIATE PLASTICS BIODECONSTRUCTION

For biological systems to deconstruct plastic waste they must first access the plastic surface. These interactions are inherently challenging, as hydrophobic plastic surfaces are poorly compatible with the charged surfaces of proteins and cells.[64] This incompatibility helps explain why plastic hydrophobicity is one of the strongest predictors of its environmental persistence.[65] To overcome this barrier, two complementary approaches can be employed (1) using interfacial forces and/or protein binding domains to enable biocatalyst interaction with highly hydrophobic plastic surfaces and/or (2) charge compatibilization of plastic-active enzymes to promote direct plastic binding. The first approach is effective against plastics that are highly hydrophobic, in which attraction is largely a function of dispersion forces. The second approach is more specific to plastics that possess a surface charge, where binding can be achieved via dipole interactions. Below, we review several techniques to implement these strategies at both the cellular and enzymatic levels.

Whole-cell biocatalysts that adhere to plastic surfaces localize enzymatic activity at the interface. The most well-characterized microbial adhesion phenotype is biofilm formation.[66–68] This action is mediated by cell charge and various secreted extracellular polymeric substances (EPS) which comprise the biofilm matrix.[69] However, not all biofilm-forming microbes bind effectively to all plastics.[70] Biosurfactants play a particularly active role in this surface colonization.[71] For example, the alkane-degrading bacterium, *Alcanivorax borkumensis*, forms robust biofilms on LDPE surfaces, resulting in significant weight loss of the plastic.[72] The compatibility of *Alcanivorax* to a highly hydrophobic plastic like LDPE stems from the glycine-glycolipid biosurfactant they produce.[8] Similarly, fungal biofilms utilize amphiphilic proteins known as hydrophobins to bind hydrophobic substrates.[73] *Aspergillus* species expressing hydrophobins can rapidly bind and flocculate a wide range of plastics, including HDPE, LDPE, PS, and PET, often within seconds.[74] However, these chassis are non-model, and more robust genetic tools are needed to develop them into whole-cell biocatalysts.

Once a microbe has adhered to a plastic surface it must make its enzyme payload available in the extracellular space to access the polymer substrate. Many naturally-occurring plastic-degrading organisms rely on extracellular secretion of plastic-active enzymes. *Ideonella sakaiensis* secretes IsPETase, which hydrolyzes insoluble PET into soluble oligomers that can be transported into the cell for metabolism.[75] However, enzyme secretion can be a limiting step, as illustrated in cellulolytic systems, where microbes and engineered hosts have been optimized to boost secretion capacity. This was achieved primarily by either (1) engineering signal peptides which act to designate to native cell machinery which enzymes should be secreted,[76] or (2) enhancing secretory pathway flux by overexpressing Sec pathway components.[77] In microbial chassis that lack extensive genetic parts, screening N-terminal signal peptide variants for enhanced secretion by the conserved Sec pathway may be an effective strategy. An alternative to secretion is cell surface display, in which enzymes are anchored to the microbial cell envelope, localizing activity directly at the cell-polymer interface. Surface display has been widely implemented in model microbial chassis using well-characterized anchoring motifs in various bacterial and fungal hosts.[78] By tethering enzymes to the cell surface, these approaches maintain high local enzyme concentrations, reduce diffusional loss, and enable repeated or sustained interaction with insoluble substrates such as plastics.[79] The mechanisms by which a cell displays an enzyme are highly host-dependent. For example, *E. coli* was engineered to surface display IsPETase using the PgsA membrane anchor and was able to degrade BHET with sustained activity for at least 5 reaction cycles.[80] When working in genetically tractable model organisms, surface display offers a robust strategy to enhance enzyme–plastic interactions beyond what can be achieved through secretion alone.

Rather than directly engineering non-model biofilm formers, their mechanisms can inform the engineering of model organisms. For example, EPS structural stability and, by extension, biofilm mass can be enhanced with increased expression of cyclases, making them a model engineering target.[81] Overexpression of cyclases DgcC and WspR in an *E. coli* expressing PET hydrolase TfCut2 led to a 15% increase in weight loss reduction of polycaprolactone, relative to a control strain expressing TfCut2 only, likely a result of greater biofilm mass[82] (Figure 2). More advanced strategies include yeast surface display, which presents proteins externally for direct plastic interaction. Co-expression of IsPETase and a class II hydrophobin from *Trichoderma reesei* on *Pichia pastoris* enabled 10.9% conversion of highly crystalline PET over 10 days, whereas IsPETase alone had no activity.[83] These results underscore the importance of pairing biosurfactants with plastic-degrading enzymes to expand substrate scope and improve deconstruction efficiency.

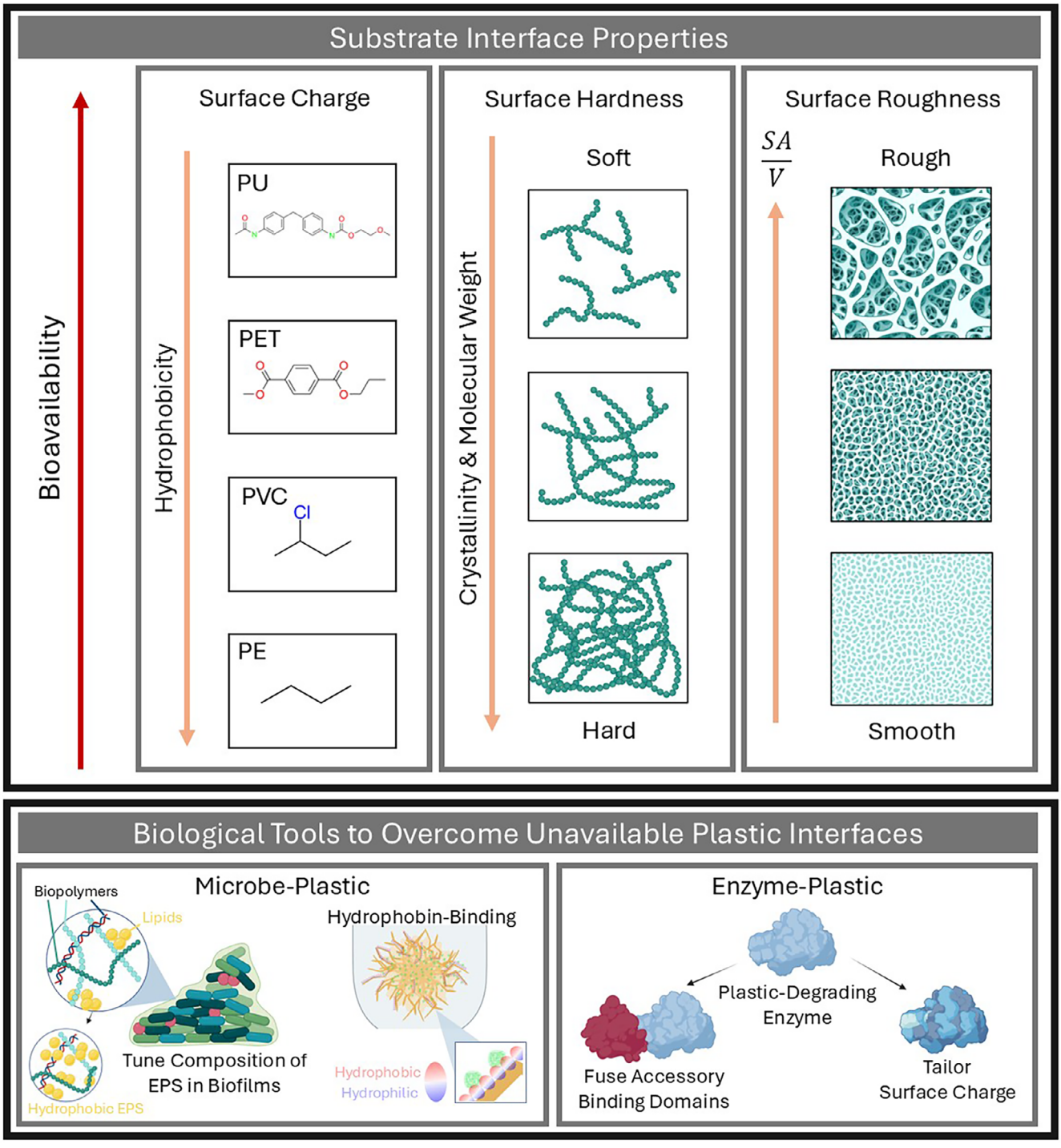

FIGURE 2 Multiscale physiochemical surface properties impact plastic bioavailability and biological tools which mediate binding.

Enzymatic binding to a plastic, and thus its deconstruction rate, is governed by protein surface features such as charge and hydrophobicity. For moderately hydrophobic plastics like polyesters and polyamides, binding is facilitated by complementary charge distributions.[84] For example, PET hydrolysis by PET2 improved 1.8-fold after seven mutations enriched positive residues near the active site, enhancing compatibility with PET's negative surface charge.[85] However, there is a tradeoff between substrate affinity and enzyme turnover. Excessively strong affinity inhibits product release, generating an enzyme-specific optimum for binding affinity in accordance with Sabatier's principle. For example, PET hydrolases from *Thermobifida fusca* and leaf-cutter compost exhibited optima at K_ds of 20 μM and 6 μM, respectively.[86] In contrast, highly hydrophobic, non-hydrolyzable plastics require hydrophobic binding domains (Figure 2). LDPE oxidation by dye-decolorizing peroxidases (DyP) was enabled by a native hydrophobic loop domain near a non-canonical surface-active site.[87] Homologs lacking this domain did not display LDPE activity, while engineered variants with extended hydrophobic loops exhibited up to a 100% increase in oxidation. Similarly, fusing hydrophobic binding modules from cellobiohydrolase I and polyhydroxyalkanoate depolymerase to a cutinase from *Thermobifida cellulosilytica* enhanced PET surface absorption and tripled deconstruction efficiency.[85] These modular domains, combined with rational engineering efforts such as recombinant accessory domains and bulk surface charge tuning, offer a broad design space for developing high-performance plastics-active enzymes.

While the biotic properties above mediate plastic adhesion, abiotic factors, such as polymer chemistry and environmental conditions, also define the limits of interaction. Plastics span a spectrum of hydrophobicity, necessitating that binding activity is established for each polymer type. For example, polyesters and polyamides are less hydrophobic than polyolefins as they contain several polar functional groups in their backbone[65] (Figure 2). Additive loading, contamination, and environmental factors further influence biomolecular binding.[88] To isolate base binding activity, biodeconstruction studies should use additive-stripped plastics and minimal buffers, when possible. Physical properties such as surface roughness and hardness (i.e., crystallinity and molecular weight) also impact binding at micron scale interfaces[89] (Figure 2). These variables should be defined and standardized across substrates to establish a baseline for binding performance.

4 | BIOCATALYSTS MUST BE DISCOVERED AND ENGINEERED FOR EFFICIENT BIODECONSTRUCTION

At the heart of many chemical engineering processes is an efficient catalyst. Effective biodegradation requires specific catalysts for each step of the deconstruction pathway tailored to each plastic type. Several of these catalysts already exist in nature for many plastics, as evidenced by the reported deconstruction of all major types of plastics by various microorganisms and insects. A comprehensive list of plastic-deconstructing microbes and enzymes can be found in a recent review.[40] Notable examples include IsPETase from *Ideonella sakaiensis*[90] and leaf-branch compost cutinase (LCC),[6] both of which rapidly depolymerize PET into the dimer, bis-(2-hydroxyethyl) terephthalate (BHET) and monomer, mono-(2-hydroxyethyl) terephthalate (MHET). These intermediates can be further processed by BHETase and MHETase to generate terephthalate and ethylene glycol that can be recycled back into new PET[90–92] or upgraded to other chemicals.[93–95] The discovery of IsPETase has catalyzed a wave of plastic-active enzyme engineering efforts, accelerating the development of industrial-scale enzymatic PET recycling in less than a decade since its initial characterization.[6]

Efficient enzymes for the deconstruction of non-PET plastics remain largely elusive, often due to the use of nonideal starting substrates and inconsistent or non-quantitative material characterization. For example, engineered nylonases have demonstrated limited activity, deconstructing only 0.67% of the tested polymer.[96] However, the addition of fresh enzyme did not increase the reaction extent, suggesting that the substrate itself lacked sufficient accessible hydrolyzable bonds to properly quantify enzyme activity.[96] Similarly, polyurethane esterases have been identified on the basis of their activity on soluble substrate mimics, but their deconstruction performance on actual polymers remains unquantified.[97–100] This gap reflects a broader issue: the absence of standardized methodologies to rigorously qualify and quantify biological plastics deconstruction. As a result, claims of enzymatic deconstruction of non-hydrolyzable plastics such as low-density polyethylene (LDPE) are often met with skepticism. These reports typically rely on indirect detection methods, such as Fourier-transform infrared spectroscopy (FTIR), which can produce false positives due to enzyme-derived artifacts (e.g., functional groups in amino acid residues that mimic degradation signal).[101,102] Moreover, results are often not generalizable across similar substrates due to uncharacterized variability in substrate properties.[103] Additives further complicate analysis. Many resemble plastic degradation products and can leach from the plastic, confounding techniques like gas chromatography–mass spectrometry (GC–MS) and leading to misleading signals of deconstruction.[104,105] To confirm enzymatic plastic degradation, direct methods should be prioritized. These include the use of isotope-labeled plastic substrates and gel permeation chromatography (GPC) to track molecular weight changes and label degradation products.[101] When direct methods are not feasible due to resource or cost limitations, indirect methodologies such as differential scanning calorimetry (DSC), FTIR or x-ray photoelectron spectroscopy (XPS) may be used with rigorous controls, including inactive enzyme treatments and careful interpretation to minimize false positives and ensure reliable conclusions.[101]

Given the absence of truly efficient enzymes for deconstructing plastics beyond PET, a systematic approach, integrating both top-down and bottom-up methodologies, is essential for identifying new biocatalysts. Microbial communities from landfill soils and gut microbiomes of plastic-deconstructing insects are particularly promising sources due to their prolonged exposure to plastics or structurally similar molecules such as long-chain alkanes. These environments offer high biodiversity and strong evolutionary pressure, increasing the likelihood of discovering substrate-promiscuous enzymes.[40]

A notable example is the discovery of *Ideonella sakaiensis* from a PET bottle recycling facility, which led to the identification of IsPETase.[90] In this instance, a bottom-up approach was taken, where microorganisms were cultivated from soil samples with PET as their sole carbon source followed by isolation and screening for plastic-degrading activity.[90] While effective, bottom-up strategies are inherently limited by the fact that over 99% of microorganisms are uncultivable.[106] To overcome this limitation, top-down approaches are critical as they provide access to enzymes from the vast uncultured microbial majority and expand the scope of discovery beyond what cultivation-based methods can achieve.

In a top-down enzyme discovery approach, multi-omics techniques are used to identify biomacromolecules associated with plastic deconstruction phenotypes at the genomic, transcriptomic, and proteomic levels. These methods provide insight into the DNA, RNA, and proteins associated with deconstruction processes. Most definitive of these is proteomics, as the proteins actively expressed by microorganisms to deconstruct plastics will be present in samples undergoing degradation.[107,108] Genomic and transcriptomic data complement proteomic analyses by helping to identify the microbial taxa and genes that are enriched or upregulated in plastic-deconstructing communities. While multi-omics can generate strong hypotheses about candidate enzymes, these remain putative until validated experimentally. To confirm activity, enzymes must be expressed, purified, and tested directly on relevant plastic substrates. Only through such direct assays can their true biodegradation potential be established.

The activity of naturally occurring plastic deconstructing enzymes will need to be engineered to achieve industrially relevant levels, as demonstrated by the development of high-performance PET hydrolases.[13,14,92] In natural environments, plastics are unlikely to be the preferred substrates for these enzymes due to their insolubility and hydrophobicity. Therefore, plastic-active enzymes are often substrate-promiscuous enzymes that canonically act on structurally similar natural polymers or hydrocarbons, such as those in alkane metabolism.[40,47] Once a plastic-active enzyme is identified, directed evolution can be used to enhance its activity on the target plastic.[109] This process involves generating libraries of enzyme variants and selecting those with improved performance. One practical approach is to express these variants in a heterologous host capable of growing on the plastic substrate only with the library, using growth rate as a proxy for enzymatic activity. Alternatively, purified enzyme variants can be screened directly on plastic substrates, though this method is typically low-throughput due to the lack of parallelizable assays for non-PET plastics. To accelerate enzyme discovery and optimization, high-throughput screening methodologies must be developed.[110] These should detect chemical changes required to deconstruct a plastic, such as oxidation of non-hydrolyzable plastics or the release of specific monomers or functional groups (e.g., chlorides from polyvinyl chloride (PVC) or styrenes from polystyrene).[111] The use of high-throughput HPLC detection of PET deconstruction products enabled the creation of evolved PET hydrolases 4–75 fold more active than wildtype IsPETase,[31,112] pushing enzymatic performance towards industrial relevance.

Artificial intelligence and machine learning (AI/ML) approaches have emerged as powerful tools for engineering enzymes, often outperforming traditional directed evolution.[113] In the context of plastic-degradation, machine learning algorithms have improved IsPETase activity more than 60-fold relative to wildtype.[13] Among ML techniques, large language models (LLMs) use sequence data to identify optimal amino acid substitutions from vast libraries, enhancing enzyme performance.[114] However, models that incorporate protein structural and biophysical principles tend to yield superior results, as they are informed by the underlying biochemical interactions within the protein. For example, the most active PET hydrolases to date, FAST-PETase[13] and TurboPETase,[14] were developed using ML-guided strategies focused on enzyme stability. FAST-PETase does so by incorporating ML-derived rules to suggest mutations that stabilize the local microenvironment of specific residues.[13,115] TurboPETase combined LLM-derived mutations with intramolecular force-field calculations to optimize both thermostability and catalytic activity.[14] These engineering objectives, such as enhancing thermostability, optimizing pH tolerance, and improving substrate binding, are broadly applicable to enzymes targeting non-PET plastics. However, the development of robust ML models for these plastics is currently limited by insufficient training data. This underscores the need for high-throughput screening methodologies to accelerate the discovery and characterization of plastic-active enzymes. Therefore, to engineer efficient catalysts for plastics biodeconstruction, enzymes should be (1) discovered from environments where plastics deconstruction occurs naturally; (2) tested on additive-free, low-crystallinity, low-molecular weight plastics using high throughput, when possible to detect bona fide polymer deconstruction; and (3) engineered to be effective against environmentally representative plastics for industrial relevance using directed evolution and/or rational approaches including AI/ML (Figure 3). This integrated strategy will be essential for expanding enzymatic solutions beyond PET and enabling scalable biological plastic recycling.

To realize biological plastics deconstruction at scale, enzymes must be engineered not only for improved catalytic activity but also for compatibility with the industrial conditions required to effectively break down plastics. In other words, the deconstruction process must be looked at holistically when designing enzymes for industrial use, accounting for factors such as temperature, pH, and solids loading. The most effective enzyme for PET degradation at room temperature in a laboratory setting may not be suitable for industrial applications where increased temperatures and pHs are used to decrease crystallinity and improve biodeconstruction.[116] As PET deconstruction has moved from bench-scale to industrial bioreactors, enzymes have been engineered to function optimally at 60–70°C[13,14,117] and under high solids loading conditions.[14] As efforts to biologically deconstruct non-PET plastics advance beyond the lab, it is essential to consider the crystallinity and molecular weight regimes of each plastic type. Activity assays should be conducted with environmentally representative polymer substrates with realistic molecular weight, crystallinity, and additive content after initial discovery and characterization on model substrates. Enzymes must be tailored to operate within the bounds of

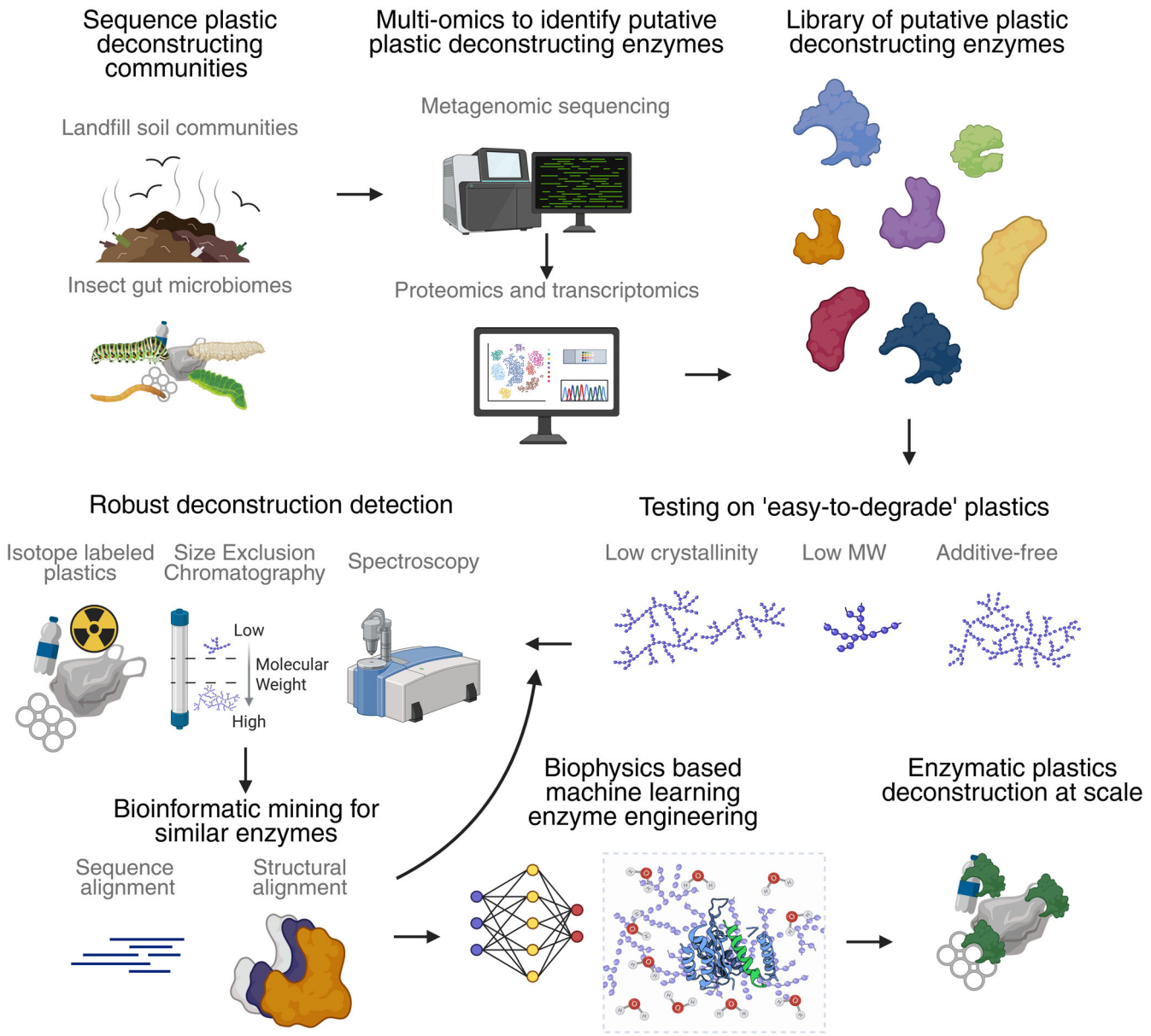

FIGURE 3 Workflow for discovering and engineering enzymes for plastics biodeconstruction.

these material properties under industrially relevant conditions. This approach ensures that enzyme performance is not only effective in controlled environments but also scalable and robust in real-world processing systems.

The deconstruction of non-hydrolyzable plastics likely requires multiple enzymes acting in concert to break down the polymer backbone,[40] in addition to enzymes needed to degrade processing additives. Therefore. processes must be engineered wherein these enzymes can work synergistically to most efficiently deconstruct the plastic, minimizing transport limitations and accelerating reaction rates. One strategy involves spatial organization of enzymes, positioning them in close proximity to facilitate sequential reactions.[118] For example, PETase and MHETase enzymes have been co-immobilized on magnetic nanoparticles at optimized stoichiometric ratios, resulting in a > 2.5-fold improvement in PET deconstruction compared to free enzymes.[119] Similarly, DNA or protein based scaffolds can be used to dock enzymes in a defined sequence, mimicking natural enzyme cascades in microbial metabolism.[118] This design allows the polymer to be "passed" from one enzyme to the next, enhancing deconstruction kinetics by eliminating reliance on random collisions in a well-mixed reactor. Such modular, scaffolded systems offer a promising route to improve the efficiency of plastic biodegradation, especially for complex polymers requiring multi-step enzymatic breakdown.

5 | PERSPECTIVE

Plastics deconstruction must be approached holistically to enable valorization of plastic waste, considering the chemical and physical complexity of the material. Plastic components, namely the polymer(s) and any additives, require distinct and potentially incompatible deconstruction technologies. For example, certain plastic additives are

known to inhibit inorganic catalysts for polyolefin deconstruction,[41] necessitating the development of specific strategies for their removal or transformation. Even the polymer itself should be viewed as a heterogeneous system, with chains spanning a broad range of molecular weights and exhibiting regions of varying crystallinity. These differences in mechanical and structural properties result in chain-to-chain variability in deconstruction potential. Moreover, different enzymatic or chemical technologies may be selectively effective within specific crystallinity or molecular weight regimes. This is demonstrated by PET hydrolases, which preferentially degrade amorphous polymer regions while leaving crystalline domains largely intact.[36] To design effective and scalable deconstruction technologies, it is essential to match the catalytic strategy to the material characteristics of each plastic component. This systems-level perspective ensures that the resulting deconstruction products are compatible with downstream valorization pathways and that the process is both efficient and adaptable across diverse plastic waste streams.

Biological solutions for the deconstruction of plastics are particularly promising due to their tunability and selectivity. Enzymes can be engineered to target both polymer chains and associated additives,[40] enabling breakdown of each component in a plastic waste stream for eventual upcycling. However, to realize these processes at scale, biological deconstruction must be assessed systematically, addressing both binding and reactivity at each step. An enzyme must first bind effectively to the plastic surface to a plastic to react and deconstruct the substrate. Once bound, it must exhibit sufficient processivity to degrade the entire substrate. This often requires pre-treatment to reduce molecular weight, crystallinity, and additive loading, thereby enhancing bioavailability and enabling scalable biodeconstruction. Because plastic deconstruction typically involves multiple enzymatic steps, each enzyme must be evaluated independently to validate its specific biochemical role. These steps must then be integrated into a cohesive bioprocess, optimized for industrial conditions such as solids loading,[14] pH,[6] and temperature.[31] Enzymes will likely need to be engineered to remain active under these conditions. Moreover, each step in the process should be treated as a unit operation, with potentially distinct optimal operating conditions. Some steps in the process that are difficult biologically, such as the oxidation of polyolefins required for deconstruction,[87] may require hybrid chemical and biological approaches. To determine the most effective combination of biological and chemical technologies, techno-economic analyses should be conducted. Once robust biological technologies are developed for each component of the plastic waste stream, they can be integrated into bio-upcycling platforms. Biologically driven plastic deconstruction can then be used to fuel bio-upcycling processes, as extensively reviewed elsewhere, to valorize plastics waste, offsetting petrochemical usage and emissions.[8,40,120]

AUTHOR CONTRIBUTIONS

Mark A. Blenner: Conceptualization; funding acquisition; writing – review and editing; project administration; supervision. **Kevin V. Solomon:** Conceptualization; writing – review and editing; funding acquisition; project administration; supervision. **Ross R. Klauer:** Conceptualization, Writing – original draft, Writing – reviewing & editing. **Nathan N. Miller:** Conceptualization, Writing – original draft, Writing – reviewing & editing.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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