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# Applications of synthetic polymers directed toward living cells

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Cells execute remarkable functions using biopolymers synthesized from natural building blocks. Engineering cells to leverage the vast array of synthesizable abiotic polymers could provide enhanced or entirely new cellular functions. Here we discuss the applications of in situ-synthesized abiotic polymers in three distinct domains: intracellular polymerization, cell-surface polymerization and extracellular polymerization. These advances have led to novel applications in various areas, such as cancer therapy, cell imaging, cellular activity manipulation, cell protection and electrode assembly. Examples of these synthetic approaches can be applied across all domains of life, ranging from microbes and cultured mammalian cells to plants and animals. Finally, we discuss challenges and future opportunities in this emerging field, which could enable new synthetic approaches to influence biological processes and functions.

Cell-based polymerization is a promising approach to bridging the gap between synthetic chemistry and biological systems, offering a gateway to building functional materials and devices directly within living tissues. Despite the challenges of performing exogenous chemical reactions in biological systems, recent progress has demonstrated that, by leveraging cellular machinery, native chemical environments and external stimuli, researchers can tailor reaction conditions with precise control over the properties, structures and locations of synthesized polymers. Compared to the established process of introducing prefabricated materials[1–5], the in situ synthesis of functional polymers on living cells shows signs of improved integration with the cellular microenvironment, alleviating disparities of topography, chemistry, mechanical attributes and electrical characteristics at the interface between the material and cells. This emerging field could impact many biomedical research domains, ranging from regulating cell behaviour to targeted therapeutic interventions.

Synthetic biology has enabled the modification and regulation of biopolymer synthesis from natural building blocks[6–8]. However, the complexity of genetic circuits, limited diversity of natural precursors, and incompatibility with many mammalian systems restrict the range of functionalities achievable through biomolecules synthesized strictly from natural precursors. Non-natural precursors, in comparison, offer vastly wider possibilities for molecular design and functionalization, but must be chosen carefully to avoid unwanted cytotoxicity.

The synthesis of abiotic functional polymers directly on living cells necessitates careful consideration of several factors. First, the selection of reactants and reaction triggers determines the nature and kinetics of polymerization. The monomers should be soluble in physiological environments, and the reaction should be controlled by endogenous chemical environments or external stimuli, such as redox agents, enzymes or light. Second, precisely targeting reactions to specific locations, such as the cytosol, cell surface or extracellular space, ensures that the desired functionalities are achieved while minimizing off-target effects. For instance, in the case of intracellular polymerization, monomers should be membrane-permeable and locally enriched, whereas the polymers should be retained within the cell. For cell-surface engineering, approaches such as electrostatic interaction, chemical bonding and genetic engineering have been demonstrated to anchor monomers, initiators, catalysts and polymers onto the cell surface. For extracellular polymerization, where the reactions take place is determined primarily by how fast and how far the reactants diffuse into the tissue. Third, a hurdle in incorporating abiotic organic

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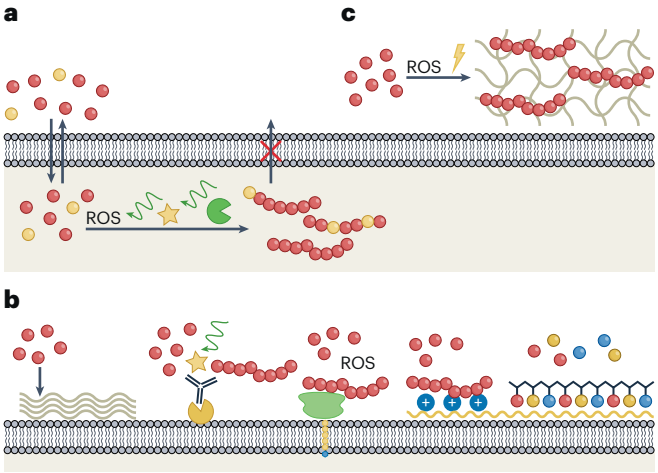


**Fig. 1 | Conceptual overview of abiotic polymer synthesis on living cells.** **a**, Intracellular polymerization, achieved by delivering membrane-permeable monomers to the cell, leading to the in situ formation of polymers retained within the cell. Reaction triggers include ROS, light, photosensitizers and enzymes. **b**, Cell-surface engineering, enabled by localizing the polymerization reaction to the cell surface through cell-templated synthesis, membrane-anchored enzymes and surface-bound initiators. **c**, Extracellular polymerization in tissues can be initiated by ROS or electricity.

chemistry into living systems lies in the potential reaction instability and cytotoxicity within physiological environments. Depending on the application, researchers need to evaluate the impact of polymerization reactions on cell viability. For live-cell applications, both the reactions and the synthesized polymers must be biocompatible. For applications focused on cell ablation, the reactions should evoke acute, localized cytotoxicity within only the targeted cells.

This Review summarizes controlled strategies to synthesize abiotic polymers within living environments to impact cell function. We focus on the synthesis of abiotic polymers in three distinct domains: intracellular polymerization, cell-surface polymerization and extracellular polymerization (Fig. 1), and discuss the methodologies, challenges and unique biomedical applications enabled by each of these domains. This Review contributes to a deeper understanding of the emerging field of cell-based polymerization and its innovative applications in biomedicine, biotechnology and beyond (Table 1).

## Intracellular polymerization

The intracellular polymerization of non-natural building blocks permits the introduction of entirely novel means to control cellular function and behaviour. This approach mirrors the natural synthesis of biopolymers such as nucleic acids, proteins and polysaccharides within the cell. It is important to note that the intricate environment inside the cell imposes several constraints on the design of non-natural reactions. First, the monomers should be membrane-permeable and biocompatible, and the polymers should be retained within the cell. Second, the polymerization reaction should be controllably triggered by a specific endogenous or exogenous stimulus. Third, depending on their goals, researchers should consider how the polymerization reactions interface with the native intracellular chemistry, for instance, whether they are biocompatible or toxic. Here we summarize recent works on cytotoxic polymerization for cancer therapy and biocompatible polymerization for cell imaging and regulation (Fig. 2).

### Cytotoxic polymerization for cancer therapy

Cancer cells exhibit elevated basal levels of reactive oxygen species (ROS) compared to normal cells, a difference that has been used as an endogenous trigger for cytotoxic polymerization reactions[9–11]. For example, it has been shown that intracellular oxidative polymerization of organotellurides triggered by the intracellular ROS can selectively induce apoptosis of cancer cells and inhibition of tumour growth in vivo (Fig. 2a)[9]. Specifically, difunctionalized organotelluride monomers have been conjugated to biocompatible gold nanoparticles, which served as transmembrane carriers and resulted in local enrichment of the monomers. ROS oxidation of Te(II) to Te(IV) polymerized these monomers via an extended Te–O chain. The polymers obtained from ROS-triggered polymerization disrupt intracellular antioxidant systems in cancer cells by interacting with selenoproteins, leading to a greater oxidative stress that in turn further increases oxidative polymerization, which eventually activates ROS-related apoptosis pathways. The mechanism of telluride interference with selenoproteins might involve telluro-selenide formation or the substitution of selenide during selenoprotein translation. Similarly, the elevated ROS in cancer cells has also been used to polymerize Y-shaped diacetylene-containing lipidated peptide amphiphile (Y-DLPA1). In this process, the lipids were constructed with diacetylene units in their tails, which underwent topochemical polymerization to join Y-DLPA1 units in a polydiacetylene chain. The resulting polymer decreased cancer-cell motility and induced apoptosis[11]. The former effect was attributed to greater intracellular viscosity from the polymer, but the mechanism of cytotoxicity is not fully understood. In addition, oxidative polymerization reactions can be targeted to specific subcellular locations[12]. Specifically, disulfide monomers containing two aryl sulfide units (Mito-1) linked to a mitochondria-targeting component, a triphenylphosphonium (TPP) moiety, can accumulate preferentially within cancer-cell mitochondria because they have elevated ROS levels. Oxidation of the aryl sulfides to disulfide linkages connects Mito-1 into a polymer, which auto-catalyses polymerization by oxidatively stressing the mitochondria and resulting in a further increase in ROS levels. The formation of large fibrous polymers in turn causes mitochondrial dysfunction and activation of necroptosis. In another targeting approach, overexpressed endogenous glutathione (GSH) and supplementary sodium ascorbate (NaAsc) in the tumour microenvironment were found to be able to reactivate metal catalysts for sustained polymerization[13]. Atom transfer radical polymerization (ATRP) catalysed by a Cu(I) complex can be performed under physiological conditions, although Cu(I) is cytotoxic. This limitation can be avoided by supplying cells with a low dose of Cu(II) complex that can be locally reduced into active Cu(I) catalysts by GSH and NaAsc, initiating the polymerization of a chemotherapy agent, acryloyl paclitaxel (Acr-PTX), into a paclitaxel-bearing polymer (poly-PTX), which prolongs the drug retention time and enhances its anti-tumour effects.

In addition to using endogenous microenvironments to trigger polymerization, external stimuli, such as light, have also proven effective[14–17]. For example, in a photoactivatable prodrug system based on intracellular photoinduced electron transfer-reversible addition-fragmentation chain-transfer (PET-RAFT) polymerization, the reaction consisted of the monomer *N*,*N*-dimethylacrylamide (DMA), a water-soluble chain-transfer agent (CTA) and the photosensitizer eosin Y (Fig. 2b)[14]. Intracellular polymerization under visible-light illumination induced cancer cell-cycle arrest, apoptosis, necroptosis, reduced motilities and significantly reduced tumour growth and metastasis in vivo. Furthermore, in situ intracellular retention or polymerization of photosensitizers enables photodynamic therapy, where ROS is generated under light illumination. As an example, tumour-targeting nanoparticles composed of a diacetylene-containing lipidated peptide amphiphile (DEVD-DLPA) and mitochondria-targeting photosensitizer (C3) have been developed for self-amplified anti-tumour therapy[15]. When exposed to light, these nanoparticles produce ROS, initiating apoptosis in cells and resulting in the activation and overexpression of caspase-3. Subsequently, the caspase-3 cleaves the DEVD sequence within the nanoparticles, causing them to undergo a transformation from nanoparticles into nanofibres and promoting the in situ polymerization of diacetylene, with C3 retained on mitochondrial membranes. Continued exposure to light was observed to lead to a

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**Table 1 | Summary of abiotic polymer synthesis on or within living cells**

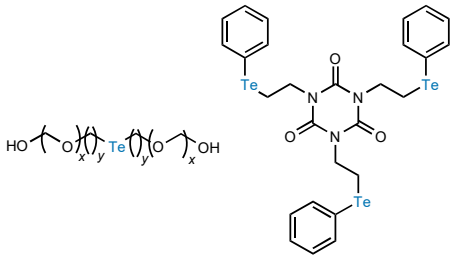
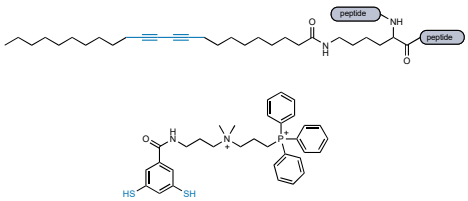
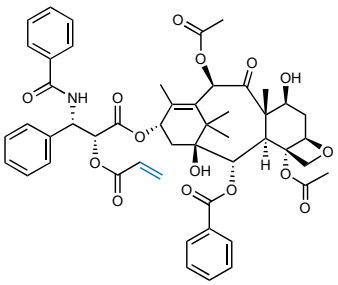
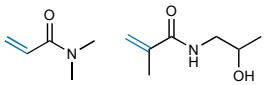
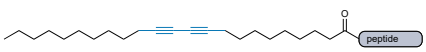
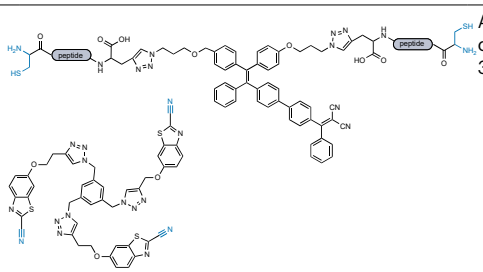
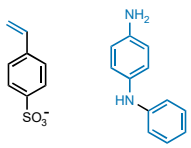
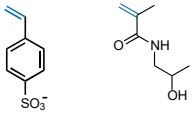
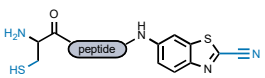
| Location | Application | Organisms | Reaction type | Monomer(s)[a] | | Reaction trigger(s) | Ref. |
|---|---|---|---|---|---|---|---|
| Intracellular | Cancer therapy | Mammalian cells, mice | Oxidative polymerization |  | Organotellurides | Endogenous ROS | 9,10 |
| | | Mammalian cells | Oxidative polymerization |  | Diacetylene-containing peptide amphiphile, disulfide derivative | Endogenous ROS | 11,12 |
| | | Mammalian cells | ATRP |  | Acryloyl paclitaxel | Endogenous GSH, NaAsc, Cu(II) | 13 |
| | | Mammalian cells, mice | RAFT |  | Methacrylamide derivative, acrylamide derivative | CTA, eosin Y, light | 14 |
| | | Mammalian cells, mice | Oxidative polymerization |  | Diacetylene-containing peptide amphiphile, photosensitizer C3 | Light, endogenous ROS | 15 |
| | | Mammalian cells, mice | Condensation polymerization |  | AIEgen-peptide conjugate, 3CBT | Endogenous GSH and cathepsin B | 16 |
| | | Mammalian cells, mice | Free-radical polymerization; oxidative polymerization |  | Styrene derivative, aniline derivative | Irgacure 2959, light, endogenous ROS | 17 |
| | Cell imaging and regulation | Mammalian cells | Free-radical polymerization |  | Methacrylate derivative, styrene derivative | Irgacure 2959, light | 18 |
| | | Mammalian cells, mice | Condensation polymerization |  | Peptide-conjugated aminothiol and CBT derivative | Endogenous GSH or furin | 19 |

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**Table 1 (continued) | Summary of abiotic polymer synthesis on or within living cells**

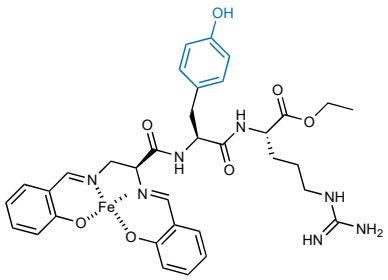
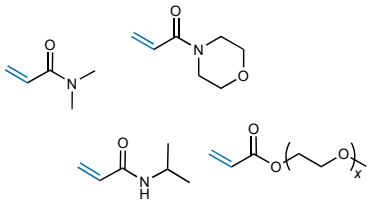
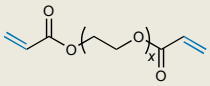
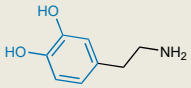
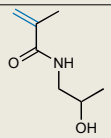
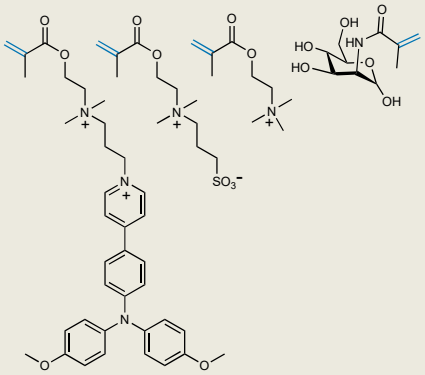
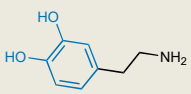
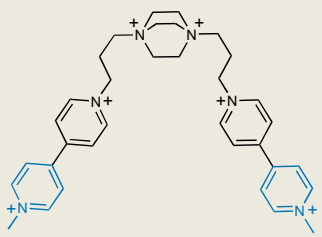
| Location | Application | Organisms | Reaction type | Monomer(s)[a] | | Reaction trigger(s) | Ref. |
|---|---|---|---|---|---|---|---|
| | | Mammalian cells | Oxidative polymerization |  | Paramagnetic tyrosine derivative | Endogenous tyrosinase | 23 |
| | | Yeast cells | RAFT |  | Acrylate derivative, acrylamide derivatives | Tyrosine residues in proteins, CTA, light | 24 |
| Cell surface | | Yeast cells | Free-radical polymerization |  | PEGDA | PEI, light, TX-Ct | 25,26 |
| | Cell viability maintenance | Bacteria, yeast cells, mammalian cells | Oxidative polymerization |  | Dopamine | Mildly alkaline solution | 27,28 |
| | | Mammalian cells | RAFT |  | Methacrylate derivative | CTA, Fe(II), $H_2O_2$ | 29 |
| | Conductivity enhancement | Bacteria, yeast cells | Oxidative polymerization |  | Pyrrole | Fe(III) | 30,31 |
| | Cell ablation | Bacteria | ATRP |  | Methacrylate derivatives | Endogenous reduction, Cu(II) | 32–34 |
| | | Bacteria | Oxidative polymerization |  | Dopamine | Mildly alkaline solution | 35,36 |
| | | Bacteria | Supramolecular polymerization |  | Viologen derivative | Endogenous reduction | 37 |

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**Table 1 (continued) | Summary of abiotic polymer synthesis on or within living cells**

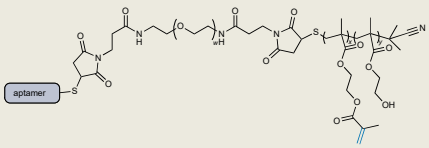
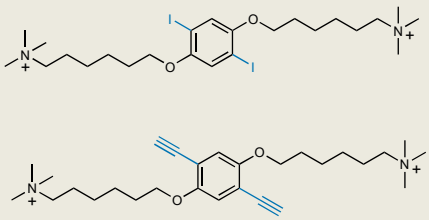
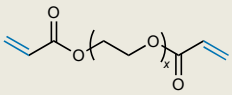
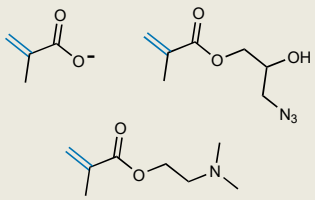
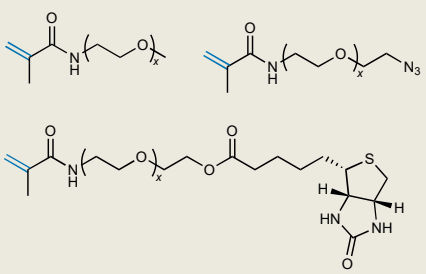
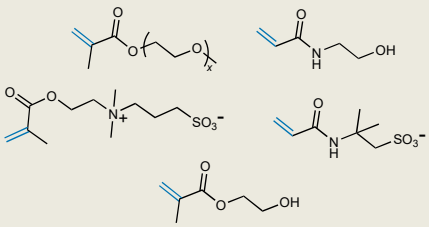
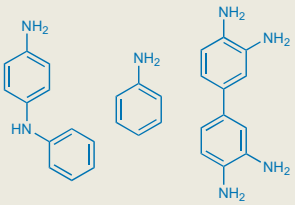
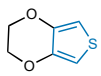
| Location | Application | Organisms | Reaction type | Monomer(s)[a] | | Reaction trigger(s) | Ref. |
|---|---|---|---|---|---|---|---|
| | | Mammalian cells | Free-radical polymerization |  | Aptamer-conjugated oligomeric methacrylate derivative | APS | 38 |
| | | Bacteria, algae | Sonogashira coupling |  | Diiodobenzene derivative, diethynylbenzene derivative | Pd(0) | 39 |
| | | Mammalian cells | Free-radical polymerization |  | PEGDA | Eosin, light | 40 |
| | | Yeast cells | ATRP |  | Methacrylate derivatives | Cu(II), PDA | 41 |
| | Cell activity manipulation | Yeast cells, mammalian cells | RAFT |  | Methacrylamide derivatives | CTA, eosin Y, light | 42 |
| | | Bacteria | ATRP |  | Methacrylate and acrylamide derivatives | Endogenous EET, Fe(III) | 43 |
| | Neural modulation | Mammalian cells, worms, mice | Oxidative polymerization |  | Aniline derivatives, DAB | Peroxidase and $H_2O_2$ or photosensitizer | 44–46 |
| Extracellular | Electropolymerization in neural tissues | Mammalian cells, mice | Oxidative polymerization |  | EDOT | Electrical potential | 48–53 |

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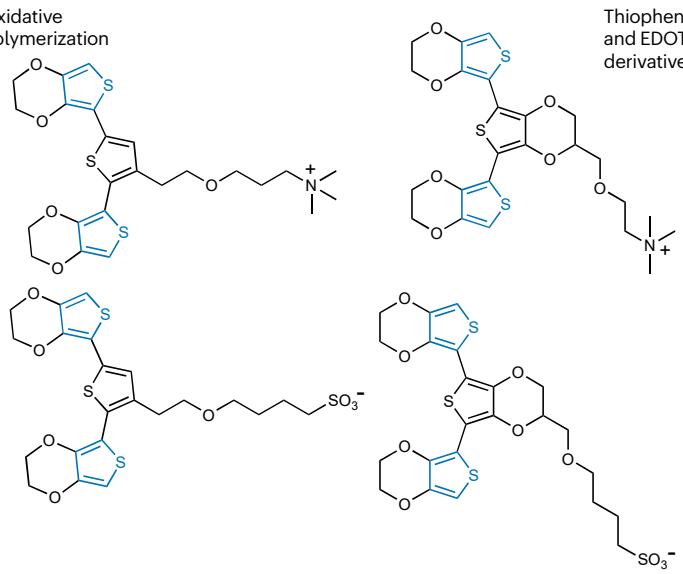
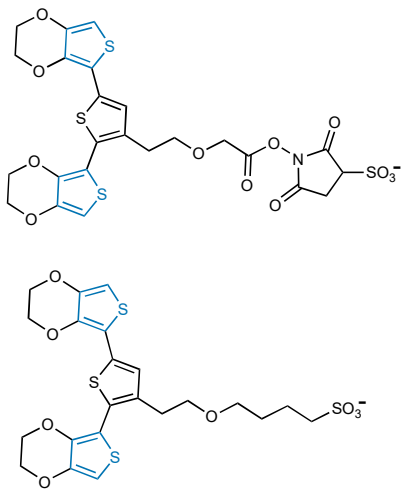
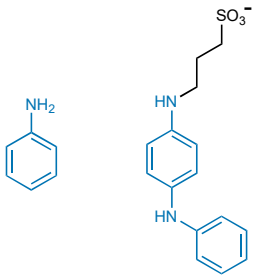
**Table 1 (continued) | Summary of abiotic polymer synthesis on or within living cells**

| Location | Application | Organisms | Reaction type | Monomer(s)[a] | | Reaction trigger(s) | Ref. |
|---|---|---|---|---|---|---|---|
| | Electrode assembly in plants | Plants | Oxidative polymerization |  | Thiophene and EDOT derivatives | Endogenous peroxidase and $H_2O_2$ | 56–59 |
| | Electrode assembly in animals | Hydra, fish, leech | Oxidative polymerization |  | Thiophene and EDOT derivatives | Endogenous or exogenous peroxidase and $H_2O_2$ | 60,61 |
| | Wound therapy | Mammalian cells, mice | Oxidative polymerization |  | Aniline derivatives | Peroxidase, endogenous ROS | 63–65 |

[a]The parts highlighted in blue undergo polymerization. 3CBT, cyanobenzothiazole-cysteine; AIEgen, aggregation-induced emission fluorogen; APS, ammonium persulfate; ATRP, atom transfer radical polymerization; CBT, cyanobenzothiazole; CTA, chain-transfer agent; DAB, 3,3′-diaminobenzidine; EDOT, 3,4-ethylenedioxythiophene; EET, extracellular electron transfer; GSH, glutathione; Irgacure 2959, 2-hydroxy-4′-(2-hydroxyethoxy)-2-methylpropiophenone; NaAsc, sodium ascorbate; NaSS, sodium 4-styrenesulfonate; PDA, polydopamine; PEGDA, poly(ethylene glycol) diacrylate; PEI, polyethyleneimine; RAFT, reversible addition-fragmentation chain transfer; ROS, reactive oxygen species; TX-Ct, thioxanthone catechol-*O*,*O*-diacetic acid.

surge in mitochondrial ROS, inducing cell apoptosis. Intracellular polymerization of another photosensitizer, aggregation-induced emission fluorogen (AIEgen), has also been observed to enable tumour imaging and light-directed treatment[16]. The AIEgen-peptide conjugate (D2P1) was cleaved by the tumour-specific cathepsin B to form D2P2, which was polymerized with cyanobenzothiazole-cysteine (3CBT). The polymers emitted strong fluorescence for cancer cell tracking, and led to actin damage and photosensitization, which enabled significant tumour reduction.

The exploration of cytotoxic polymerization strategies for cancer therapy introduces a transformative dimension to anticancer treatments. Traditional approaches like chemotherapy and radiation, while

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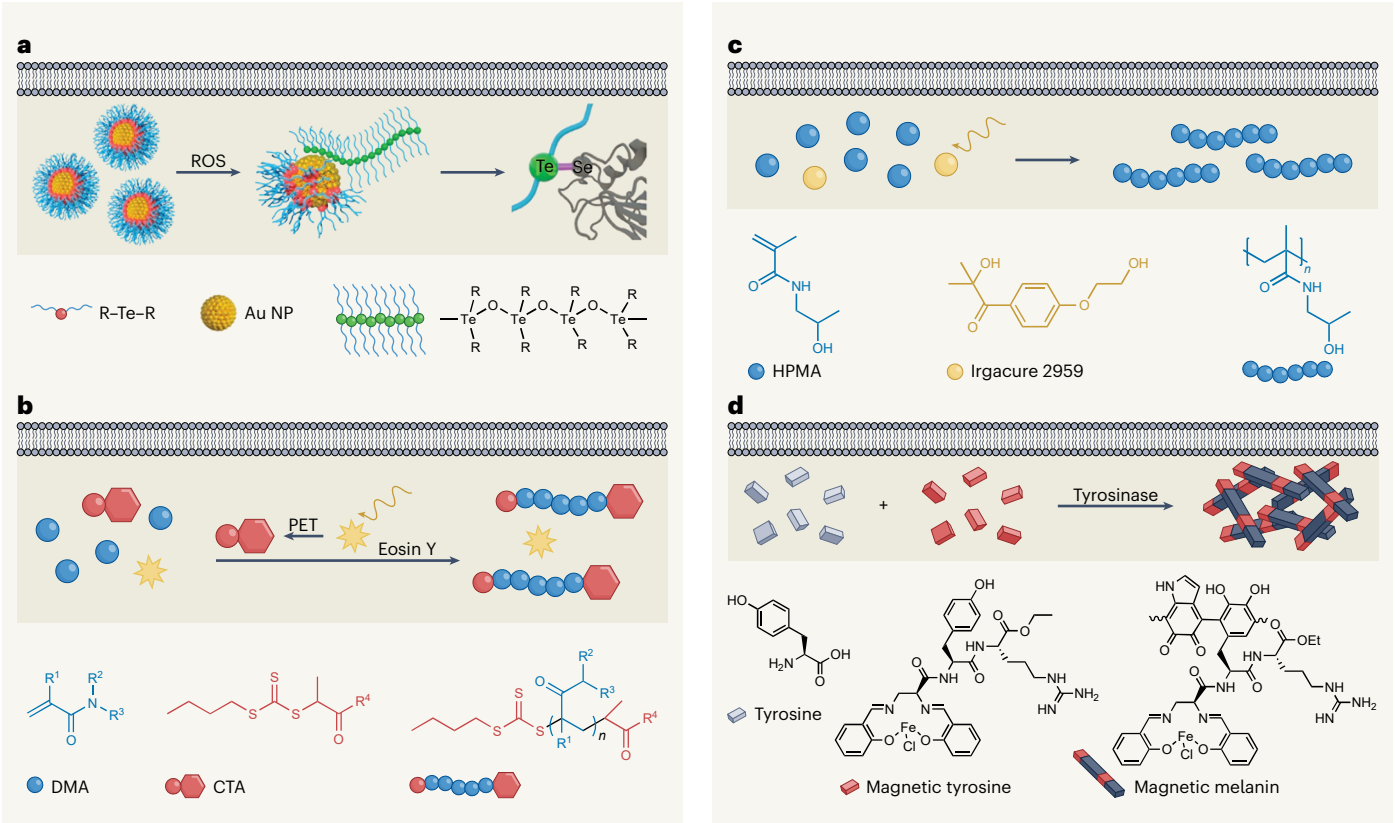


**Fig. 2 | Intracellular polymerization. a**,**b**, Cytotoxic polymerization for cancer therapy. **a**, Oxidative polymerization of organotelluride monomers (R–Te–R), delivered to cancer cells with gold nanoparticles (Au NPs), is initiated by the elevated ROS levels in cancer cells. The polymers disrupt intracellular antioxidant systems by interacting with selenoproteins. **b**, Photoinduced electron transfer-reversible addition-fragmentation chain-transfer (PET-RAFT) polymerization of DMA, assisted by a CTA and the photosensitizer eosin Y. **c**,**d**, Biocompatible polymerization for cell activity control. **c**, Radical photopolymerization of a biocompatible monomer, HPMA, with a photoinitiator, 2-hydroxy-4′-(2-hydroxyethoxy)-2-methylpropiophenone (Irgacure 2959). **d**, Oxidative polymerization of tyrosine and a magnetic tyrosine derivative is facilitated by the endogenous enzyme tyrosinase. Figure adapted with permission from: **a**, ref. 9, American Chemical Society; **c**, ref. 18, Springer Nature Ltd; **d**, ref. 23, American Chemical Society.

effective, often induce substantial adverse effects by damaging healthy cells and tissues. In contrast, intracellular polymerization, enabled by the global delivery of biocompatible monomers that polymerize locally into cytotoxic polymers that are retained only within cancer cells, holds promise for mitigating off-target effects. Despite these advantages, challenges to clinical deployment remain, such as delivering monomers in vivo, monomer toxicity, intracellular retention and clearance of polymers, and specificity in targeting selected cell types or subcellular locations. Notably, polymerization induced by high ROS levels in cancer cells may also occur in normal cells, resulting in off-target effects. For light-induced polymerization, delivering light in vivo to specific tumour sites poses a major challenge.

## Biocompatible polymerization for cell activity control

Although the intracellular synthesis of abiotic polymers holds immense promise for the fine control of intracellular processes, devising biocompatible polymerization reactions inside cells presents major challenges compared to conventional approaches such as small-molecule drugs, because it is not only the final product that must be biocompatible. Indeed, all the reactants, reaction conditions and intermediate synthesized polymers must be biocompatible, and they must all avoid unwanted interactions with the highly complex intracellular environment, unwanted impacts on cellular activity, as well as off-target effects on gene expression.

In one work that achieved intracellular radical photopolymerization, the reaction was composed of biocompatible acrylate monomers, such as *N*-(2-hydroxypropyl) methacrylamide (HPMA), and a photoinitiator, 2-hydroxy-4′-(2-hydroxyethoxy)-2-methylpropiophenone (Irgacure 2959), that was stable in the presence of oxygen and cellular components (Fig. 2c)[18]. Under illumination by 365-nm light, the polymerization achieved a conversion rate of ~68%, with minimal impact on cell viability. There was no significant change in cell proliferation for cells with polymers compared to untreated cells, but as intracellular polymerization increased cellular viscosity, it triggered actin clustering and slowed down cell migration. Incorporating fluorescent entities through co-polymerization (for example, rhodamine B acrylate), yielded highly fluorescent polymers that endured for more than five passages. This biocompatible approach to intracellular polymerization presents a versatile platform capable of modulating cellular motility and facilitating cell labelling for long-term tracking studies.

Another biocompatible intracellular polymerization of imaging agents was achieved with cysteine-cyanobenzothiazole (CBT) condensation[19,20]. This reaction was first demonstrated by designing monomers containing a CBT group and a protected aminothiol moiety[19]. Depending on the monomer design, the aminothiol was exposed under the control of either disulfide reduction by intracellular GSH or protease cleavage by intracellular furin. The exposed aminothiol reacted with the CBT group and produced luciferin derivatives, which were used for direct imaging of the proteolytic activity of furin. This intracellular polymerization system was later optimized to encourage linear polymer growth in living mice[20]. Specifically, the monomer was synthesized by covalently attaching a disulfide-protected cysteine and a CBT group to a rigid glucosamine linker. After activation

of the disulfide linkage on the cysteine by GSH, the glucosamine linker promoted the elongation of linear polymers over the formation of by-products, such as cyclic dimers. In vivo polymerization was carried out in mice with GSH-pretreated tumours, which enabled fluorescence and photoacoustic imaging of the tumour sites.

Other works in this field have used amino acids or their derivatives as monomers for intracellular polymerization[21–24]. For example, the endogenous cellular machinery for synthesizing melanin was used to synthesize magnetic melanin (Fig. 2d)[23]. Animal melanin, a non-soluble pigmented polymer, is generated within melanosomes via oxidative polymerization of tyrosine, facilitated by the enzyme tyrosinase. A water-soluble paramagnetic tyrosine derivative, m-YR, was synthesized by conjugating a tyrosine–arginine dipeptide with *N*,*N*′-bis(salicylidene)ethylenediamine-iron(III) complex, an organoiron compound often used in magnetic hyperthermia anticancer therapy. In the presence of a magnet, the melanoma cells that incorporated m-YR into their intracellular melanin elongated and aligned themselves parallel to the magnetic power lines. This reaction could form the basis to explore mechanobiology and magnetogenetics.

## Cell surface engineering

Cell–environment interactions are primarily regulated by cell membranes. Engineering the membrane surface through in situ polymerization creates an artificial extracellular matrix (ECM), which holds the potential to exert control over cellular interactions, behaviours and functions. Compared to the intracellular environment, significantly more reactions are biocompatible with the cell surface, as the intact membranes or cell walls are not permeable to larger reactants, and the reactions are less likely to interfere with (or face interference from) native intracellular processes. Surface engineering holds immense potential for applications in biomedicine, as evidenced by studies showing it can sustain cell viability, control activity, facilitate imaging and enable targeted ablation (Fig. 3).

The polymerization mechanisms and material properties have been tailored to accommodate a diverse range of applications. For example, free-radical polymerization reactions of acrylates and methacrylates are commonly used due to their finely tunable structure. This approach allows for the co-polymerization of multiple monomers, facilitating gradients in functionality. Controlled radical techniques, such as ATRP and RAFT, provide precise control over molecular weight. In addition, oxidative polymerization reactions typically yield aryl–aryl or aryl–heteroatom bonds. Although this route requires stoichiometric oxidation, and is generally performed with a single monomer, it offers access to conjugated polymers, such as polypyrroles and polyanilines, and polymers derived from native biomolecules, such as polydopamine, that are not attainable through free-radical polymerization.

A critical consideration in surface-initiated polymerization is how to confine the reaction and the synthesized products to the surface, both to minimize off-target effects on the intracellular machinery and to maximize product availability on the membrane. Although straightforward methods like electrostatic attraction are suitable for scenarios requiring global modifications, such as cell protection, they often pose challenges in achieving precise spatial control. Finer control can be achieved through approaches such as metabolic labelling to target diverse surface molecules, as well as genetic and antibody targeting of distinct cell types. These techniques become important when selective modification, such as cell-type-specific neural function modulation or cell-specific ablation, becomes necessary. The choice of catalyst and initiator depends on the specific application. For instance, iron initiators are sufficient for non-targeted oxidative polymerization, but achieving cell type specificity requires genetically targetable peroxidases. In radical polymerization reactions, ARGET ATRP (activator regenerated by electron transfer atom transfer radical polymerization) leverages the natural reducing ability in the cellular environment, while RAFT allows for spatial control by tethering its chain-transfer agents to the membrane surface.

### Cell protection

Coating living cells with synthetic shells has the potential to shield the cells from harsh environments[25–29], a technique akin to the protective exosporium coat secreted by sporulating bacteria. For example, yeast cells that were surface-absorbed with polyethyleneimine (PEI) could enable graft polymerization of crosslinked poly(ethylene glycol) diacrylate (PEGDA) under visible-light irradiation[25,26]. The thickness and distribution of the polymer shells could be regulated by adjusting factors such as irradiation duration, light intensity and reactant concentration. The yeast cells encased in polymer shells showed a substantial delay in division and enhanced resistance against lysis by lyticase, both of which were tunable by controlling the shell morphology. Alternatively, polydopamine (PDA), a natural polymer inspired by adhesive mussel-foot proteins, has also been used as a cytoprotective coating (Fig. 3a)[28]. Because cell membranes invariably exhibit amine, thiol and hydroxyl groups, PDA can adhere to the cell surface through either covalent or hydrogen bonds. The oxidative polymerization of dopamine was achieved by incubating the cells with dopamine in a mildly alkaline solution at room temperature. The introduction of additional functional molecules, such as small-molecule fluorophores, facilitated fluorescent imaging of the treated cells. This coating methodology was successfully demonstrated on a variety of cells, including bacteria, fungi and mammalian cells, with minimal impact on cell viability and bioactivity. Notably, gut microbiota coated with PDA displayed increased resilience against gastric acid and bile salts, resulting in a sixfold increase in survival within the mouse stomach and more than a 30-fold increase in bioavailability in the gut, in comparison to uncoated bacteria[28]. Additionally, these coated cells exhibited a fourfold higher accumulation in diseased tissue, indicative of their targeted affinity for inflamed colonic mucosa. These results showcase the potential of PDA-coated gut microbiota as an oral therapeutic approach for targeted colitis treatment.

A recent work demonstrated the application of bioorthogonal click chemistry to achieve cell-surface polymerization in mammalian cells[29]. The approach involved the introduction of azide groups at different locations (such as glycans, proteins and lipids) on the cell membrane through metabolic labelling, facilitating azide–alkyne cycloaddition for anchoring CTA, which initiated RAFT polymerization of HPMA. Post-polymerization, Jurkat T cells demonstrated robust viability, with an essentially unaltered cytoskeleton, immune activability, intracellular ROS, DNA and protein levels, as well as cellular metabolism and proliferative capacity. The site selection for polymer growth (glycans, proteins and lipids) determined the polymer retention time on the cell surface and its impact on binding of cellular glycans to lectins. Notably, polymers grown from glycans exhibited the ability to effectively hinder lectin-induced T-cell apoptosis, offering a new approach for immunomodulation.

Practical challenges and limitations of the presented approaches include the lack of cell type selectivity and the need to investigate how these coatings might alter other cellular properties, such as mechanical characteristics. Understanding these aspects will be essential for the broader applicability of cell coatings across different cell types and for addressing potential changes in cellular functionality.

### Enhancement of electrical conductivity

Coating microbes with conducting polymers could increase the conductivity between cells, which is of great interest for the development of microbial fuel cells[30,31]. Given the negative charge on the outer membranes of bacteria, Fe(III) cations were bound to the surface of bacteria through electrostatic interaction (Fig. 3b)[30]. The Fe(III) catalysed the oxidative polymerization of pyrrole on the surfaces of *Shewanella oneidensis*, *Escherichia coli*, *Ochrobactrum anthropic* and *Streptococcus thermophilus*. Importantly, the viability of these microorganisms remained unaffected following the reaction. The resulting polypyrrole (PPy) coatings effectively enhanced direct contact-based extracellular electron transfer through outer-membrane c-type cytochromes, and

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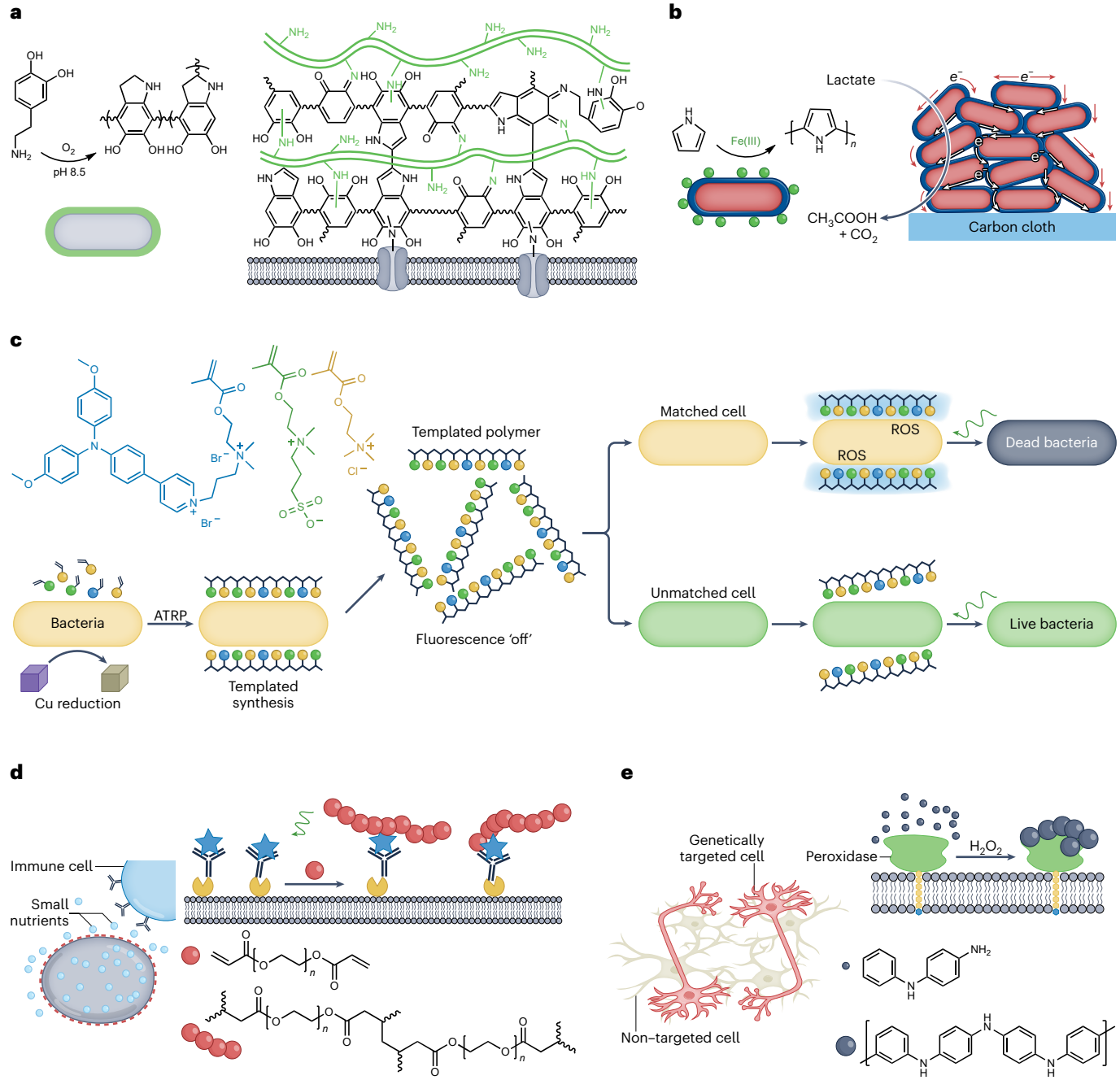


**Fig. 3 | Cell surface engineering. a**, Cell protection can be achieved through the oxidative polymerization of dopamine to form a cytoprotective coating, by incubating cells with dopamine in a mildly alkaline solution. **b**, The enhancement of electrical conductivity involves catalysing the oxidative polymerization of pyrrole by surface-bound Fe(III) cations, with bacteria coated in the resulting conductive polymer, polypyrrole, serving as anodic materials in microbial fuel cells. **c**, Selective cell ablation can be achieved through ATRP of a bacteria-templated photosensitizer polymer, catalysed by the intrinsic copper-homeostasis mechanisms. Upon recognition of the target bacteria, the polymer exhibits fluorescence and photosensitizing properties, enabling the recognition and targeted destruction of the bacteria. **d**, Manipulation of cellular activities involves enabling free-radical polymerization of PEGDA through the surface-bound photoinitiator eosin. The synthesized nanoscale hydrogel coating allows for the selective transport of small molecular nutrients while shielding the cell from undesirable larger materials, such as immune-cell receptors. **e**, Neural activity modulation is achieved through the oxidative polymerization of an aniline dimer, catalysed by genetically encoded membrane-displayed peroxidases in neurons upon delivery of hydrogen peroxide ($H_2O_2$). The conductive polyaniline and other insulating polymers effectively modulate neural activity. Figure adapted with permission from: **a**, ref. 28, Wiley; **b**, ref. 30, Wiley; **c**, ref. 34, Wiley; **e**, ref. 45, AAAS.

improved the stability of bacterial cells. The PPy-coated biofilms were then utilized as anodic materials in microbial fuel cells. In comparison to unmodified bacteria, the biofilm electrodes coated with PPy exhibited a remarkable 14.1-fold increase in power output[30]. Future studies should prioritize investigations into the long-term stability of the fuel cells.

## Selective cell ablation

Surface polymer coatings have facilitated targeted cell ablation through templated synthesis[32–34], synthesis of polymers that can generate photothermal effects[35–37], and the biochemical effects of polymers[38,39].

First, polymers synthesized on bacteria templates could be used to selectively inhibit the targeted strain[32–34]. For example, glycopolymers

have been grafted on living *E. coli* MG1655 bacteria, utilizing the inherent reducing properties of the bacteria to facilitate ARGET ATRP[33]. The monomers for glycopolymer synthesis were 2-(methacrylamido) glucopyranose (MAG) and 2-(*N*-3-*m*,sulfopropyl-*N*,*N*-dimethyl ammonium) ethyl methacrylate (MEDSA). MAG, a monomer containing sugar, was selected for its binding capability, and MEDSA, a non-sugar, non-binding monomer, was employed as a spacer within the resulting polymer chain. The sequence of monomers in the templated glycopolymers matched the arrangement of receptor proteins on the bacterial surface. Following their isolation from the bacterial templates, the polymers exhibited substantially greater affinity for the MG1655 strain compared to control polymers synthesized in solution. Notably, when exposed to a mixture of two *E. coli* strains, MG1655 and DH5α, which possess slightly distinct genomes, the templated glycopolymers displayed selective binding affinity for MG1655, demonstrating their application as highly targeted anti-infection agents that could prevent selected bacteria from interacting with host cells. Another approach involves the creation of a templated AIEgen-type photosensitizer, through copper-catalysed ATRP, where the reaction was catalysed by the intrinsic copper-homeostasis mechanisms that reduced Cu(II) to Cu(I) (Fig. 3c)[34]. This method utilized three distinct monomers: (1) a permanent cation, [2-(methacryloyloxy)ethyl] trimethyl ammonium chloride (TMAEMC), capable of binding to the negatively charged surface of bacterial cells; (2) TMAEMC-TPAPy, an AIE moiety that exhibits minimal fluorescence in its molecular state, but displays robust emission and photosensitizing properties upon forming aggregates or interacting with target analytes; and (3) [2-(methacryloyloxy)ethyl] dimethyl-(3-sulfopropyl)ammonium hydroxide (DMAPS), a zwitterionic sulfobetaine used as a non-binding spacer. Although the polymers generated from off-target bacterial templates exhibited low fluorescence, their fluorescence was activated upon binding to the specific target bacteria. Notably, these polymers demonstrated strong and selective binding to various strains of multidrug-resistant bacteria. Upon exposure to white-light irradiation, the engineered polymers facilitated the targeted destruction of the identified bacteria.

Second, surface polymer coatings possessing photothermal effects offer a promising avenue for bacteria-targeted light-controlled cell ablation[35–37]. The facultative anaerobe *Salmonella typhimurium* VNP20009 exhibits a distinct ability to selectively target tumours due to its preference for hypoxic regions within tumour cores. Nonetheless, the limited efficacy in suppressing tumours and the undesirable dose-dependent toxicity of VNP20009 hindered its broader clinical applications. To overcome these challenges, a potential solution involved the coating of VNP20009 with PDA, which provided the bacteria with photothermal capabilities while preserving their tumour-targeting proficiency[35,36]. Moreover, the phototherapeutic action mediated by PDA generated tumour-cell lysates that could serve as nutrients, attracting additional bacteria and thereby further improving the biotherapeutic impact of VNP20009. In vivo experiments conducted on tumour-bearing mice revealed that the coated bacteria induced apoptosis and tissue necrosis in melanoma cells, thereby inhibiting tumour growth.

Third, selective cell ablation could also be achieved using polymers with cytotoxic effects[38,39]. For example, CD20 is a well-known cancer antigen that exhibits increased expression on the membrane surface of Raji cells in non-Hodgkin lymphoma. CD20 could be targeted by anti-CD20 aptamer-conjugated macromers[38]. The polymerization of the macromers, initiated by ammonium persulfate (APS), led to the aggregation of CD20 receptors, thereby inducing apoptosis of Raji cells. This form of cell-surface receptor crosslinking, activated by cell-surface free-radical polymerization, offers a unique approach for manipulating cell functions mediated by the spatial distribution of cell-surface receptors.

The techniques described above have advanced the field of selective cell ablation through templated synthesis, offering inhibition of targeted bacterial strains or cancer cells. However, as these techniques progress, future investigations should delve into potential off-target effects on different cell types and explore the feasibility of in vivo applications.

### Manipulation of cellular activities

Coating the cell surface has a direct impact on cellular interactions with the external environment[40–43]. For example, a nanoscale hydrogel coating on mammalian cells synthesized by a free-radical polymerization reaction was used for selective transport of small molecular nutrients (Fig. 3d)[40]. In this approach, the photoinitiator eosin was initially attached to the membrane using antibody–surface antigen binding at a very low concentration (~1 molecule per $\mu m^2$), thus controlling subsequent polymer growth to form a nanothin layer. After introducing a precursor solution comprising PEGDA monomers, the eosin-primed cells were exposed to green light, resulting in a radical polymerization reaction that produced a crosslinked PEGDA film 100–200 nm thick, with a mesh size of 1.3–3.7 nm. This size-selective coating maintained high cell viability (~90%) and enabled the passage of beneficial low-molecular-weight substances, while blocking undesirable larger-molecular-weight materials. This technique holds potential for applications such as cell-replacement therapies, where it could shield functional exogenous cells from the host immune response.

In a different approach involving the grafting of cytocompatible polymers, ARGET ATRP was conducted on yeast surfaces following pre-polymerization of a protective PDA layer[41]. Conventional ATRP reactions are often cytotoxic owing to the presence of transition-metal catalysts (such as Cu(I)), organic solvents and reduced oxygen levels. ARGET ATRP was employed here as a partial solution to these issues, utilizing a cytocompatible reducing agent like ascorbic acid to reactivate the catalysts from Cu(II) to Cu(I). This approach not only reduced the required concentration of the metal catalyst but also facilitated aqueous polymerization under normal atmospheric conditions. To facilitate this, a PDA-based layer was initially deposited to introduce ATRP initiators and to protect the cells from radical attack during polymerization, maintaining a viability of ~70%. The resultant polymer coatings effectively hindered the aggregation of yeast cells when mixed with *E. coli*, and also delayed cell-division processes.

In another study, a cytocompatible PET-RAFT polymerization approach was used to grow controlled acrylamide polymers on the surface of CTA-modified living yeast and mammalian cells[42]. The polymer-modified yeast cell showed considerable aggregation upon addition of tannic acid, which interacted with the polymers through hydrogen bonding.

## Genetically targeted cell-type-specific synthesis

Multicellular biological systems, such as the mammalian brain, contain diverse cell types and exhibit complicated structural and organizational characteristics, making it challenging to establish precise electrical connections with specific cells. One strategy to address this limitation is to genetically modify specific cells within intact biological systems to facilitate the in situ synthesis of conductive or insulating polymers on the targeted cells (Fig. 3e)[44–46]. In a new field called genetically targeted chemical assembly (GTCA), we initially expressed a peroxidase, ascorbate peroxidase Apex2, in neurons as the genetically encoded enzyme that catalysed oxidate polymerization initiated by hydrogen peroxide ($H_2O_2$)[44]. The monomers utilized in the synthesis were 4-aminodiphenylamine (aniline dimer) and 3,3′-diaminobenzidine (DAB), for generating conductive polyaniline (PANI) and the insulating poly(3,3′-diaminobenzidine) (PDAB), respectively. Electrophysiological measurements in individual neuron cells verified that the deposited PANI and PDAB changed membrane capacitance, and thus altered neural activity in a cell-type-specific manner. Recently, we developed another genetic targeting approach, which placed horseradish peroxidase (HRP) enzyme exclusively on the external surface of the membrane. This substantially improved the efficiency and biocompatibility of the reaction

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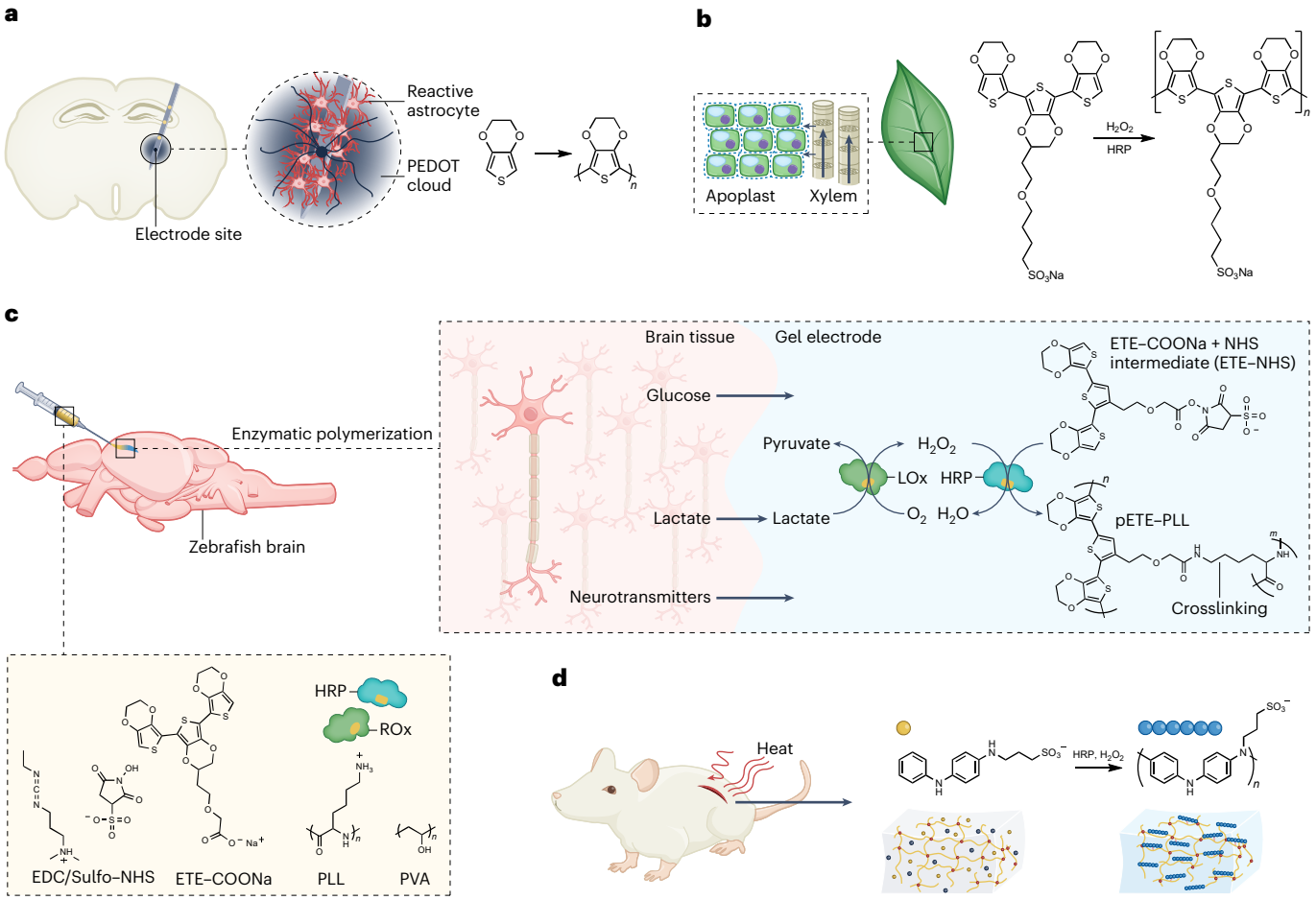


**Fig. 4 | Extracellular polymerization. a**, PEDOT is synthesized in neural tissues around the implanted electrode. This conductive polymer could improve the recording and stimulation capabilities of the electrode by bypassing glial scar encapsulation and reaching healthy neurons. **b**, In vivo electrode assembly in plants utilizes a conjugated thiophene oligomer, the sodium salt of bis[3,4-ethylenedioxythiophene]-3-thiophene butyric acid (ETE-S), serving as the precursor for generating conductive polymers catalysed by native peroxidase enzymes and $H_2O_2$. **c**, In vivo electrode assembly in animals can be achieved using a thiophene oligomer and enzymes injected into animal models. **d**, Wound monitoring and therapy can be accomplished by catalysing the polymerization of an aniline dimer derivative using the overexpressed $H_2O_2$ in infected wounds. Panels adapted with permission from: **b**, ref. 56, National Academy of Sciences; **d**, ref. 63, Elsevier. Panel **c** reproduced with permission from ref. 61, AAAS.

by placing it in the extracellular space[45]. Due to the low solubility of PANI and PDAB, these synthesized polymers formed dense deposits around neuron membranes without compromising their viability.

In HRP-catalysed polymerization reactions, cells are exposed to polymer precursor solutions without precise spatial resolution beyond genetic specificity. In addition, the HRP/$H_2O_2$ system is limited to initiating a single oxidative reaction rather than enabling continuous patterning over time. To better match the complexity and plasticity of biological structures, a genetically encoded photosensitizer, mini singlet oxygen generator (miniSOG), could be expressed in neurons, which would let researchers catalyse polymerization reactions using light illumination[45,46]. This system could enable genetically targeted 3D in vivo photolithography[47], where a laser beam could write arbitrary conductive connections or insulating shapes between the targeted cells and brain regions.

## Extracellular polymerization

In situ extracellular polymerization within biological tissues is a novel strategy for fabricating functional materials and devices for interfacing with living tissues. Unlike conventional practices involving the implantation of prefabricated polymers into the body, in situ polymerization presents an unparalleled advantage of precise control over polymer formation, structure and properties at the target site. For example, the assembly of conductive polymers within neural tissues could yield electrodes for bioelectronic interfaces. Such functional electronic materials constructed from the bottom up hold the potential for seamless integration of electronic devices into the nervous system. Here we will provide an overview of recent works including electropolymerization within neural tissues, in vivo electrode assembly in plants and animals, and the applications of polymers for wound monitoring and therapeutic interventions (Fig. 4).

### Electropolymerization in neural tissues

Brain-implanted recording and stimulation devices communicate with neurons using electrical signals, necessitating continuous and direct contact with targeted cells. However, the brain naturally generates an electrically insulating glial scar in response to foreign substances, which interferes with the transmission of electrical signals between the device and the neurons, diminishing the device's ability to accurately record neural activity or deliver targeted stimulation. One approach to overcoming this limitation is to create a conducting polymer network that grows from implanted electrodes using in situ electropolymerization of conductive polymers, such as poly(3,4-ethylenedioxythiophene) (PEDOT; Fig. 4a). This approach was first tested on cultured neural cells, with PEDOT polymerized on the electrode surfaces, enveloping the cells and their cellular extensions[48]. Remarkably, live cells enclosed

within this conductive polymer matrix maintained their viability for a minimum of 120 h post-polymerization. Later, the same reaction was carried out in mouse brains and peripheral nerves[49–51] without a significant loss of functions[52], although the chronic effects should be better characterized[53]. Through in situ polymerization, an electrically conductive network was generated, seamlessly integrating with the adjacent tissues via PEDOT filaments projecting from the electrodes. These filaments could extend deeply into the surrounding tissues, bypassing glial scar encapsulation and reaching healthy neurons.

Recent years have witnessed substantial progress in brain implants through increases in substrate flexibility and reduction of feature size to address chronic immune responses. For example, mesh electronics[54], with tissue-like flexibility and a macroporous structure, have effectively prevented glial scarring after implantation. Despite these advancements, the application of electropolymerization of conductive polymers remains a viable strategy to optimize electrode performance by decreasing impedance[55].

## In vivo electrode assembly in plants

The native environments and structures of plants might be harnessed to create electronic plants. Within plants, the native concentration of $H_2O_2$ could trigger in vivo oxidative polymerization of conductive polymers, catalysed by native peroxidase enzymes such as HRP. This polymerization reaction could be tuned to form electrical conduits and electrochemical devices[56–59]. Specifically, a water-soluble conjugated oligomer, the sodium salt of bis[3,4-ethylenedioxythiophene]-3-thiophene butyric acid (ETE-S), has been used as the precursor for generating conductive polymers (Fig. 4b)[56]. Cuttings from a garden rose were submerged in the ETE-S solution. During this process, the solution was absorbed through the xylem water transport channels, facilitated by the plant's natural transpiration mechanism, ultimately reaching the leaves and flowers. Two hours after immersion, the exposed xylem in the vascular bundles displayed a darker appearance, indicating the initiation of polymerization. ETE-S dispersed throughout the entire xylem system of the rose cutting and underwent local polymerization, resulting in the formation of long-range conducting wires with conductivity reaching up to 10 S $cm^{-1}$. Subsequently, the natural configuration of the modified plant was utilized to create a supercapacitor. In this set-up, two parallel ETE-S-based polymer xylem wires were employed as separate electrodes (functioning as redox electrodes and collectors). The plant tissue in between served as the electrolyte separator. In addition, by simply watering intact plants with the ETE-S solution, the oligomers polymerized on the roots, and the plants maintained their biological functions and continued to grow and develop, with the conductivity of the roots remaining stable for four weeks[58]. In another work, three different conjugated trimers based on thiophene and EDOT or purely EDOT trimers were synthesized[59]. Each of these trimers exhibited the capacity for enzymatic polymerization under physiological pH conditions, both in vitro and in the roots of live plants. By adjusting the composition of the backbone and side chains, it was possible to finely adjust the electronic characteristics of the polymers, as well as their localization and penetration within the roots.

The incorporation of in vivo electrode assembly could enable continuous monitoring of physiological parameters, providing real-time insight into plant processes, stress responses and growth patterns. However, one notable limitation of this approach is the restricted locations where electrode assembly can be implemented within the plant. Additionally, ensuring the scalability of this technology for widespread application across diverse plant types and sizes poses another challenge. Addressing these obstacles is pivotal for establishing this approach as a robust tool for constructing plant-based devices.

## In vivo electrode assembly in animals

The enzymatic oxidative polymerization of conductive polymers could also be accomplished within both invertebrate and vertebrate animals, taking advantage of the presence of endogenous peroxidases or metabolites[60,61]. This concept was first demonstrated in *Hydra*, an invertebrate animal[60]. Exposure to ETE-S and $H_2O_2$ during incubation led to the creation of conductive polymers within cells expressing peroxidase activity and within the secreted mucus. These polymers formed electrochemically active micrometre-sized domains that seamlessly integrated into the tissues. Later, in vivo fabrication of organic bioelectronics in zebrafish and leech models was achieved utilizing endogenous metabolites to trigger a similar enzymatic polymerization within an injectable gel, resulting in the formation of conducting polymer gels with long-range conductivity (Fig. 4c)[61]. In contrast to plants and *Hydra*, the native environments within zebrafish and leeches were incapable of facilitating oxidative polymerization reactions. To address this, a new methodology was employed involving a gel blend including an ETE derivative with a 2-ethoxyacetic acid sodium-salt side chain (ETE-COONa), along with oxidase enzymes (glucose oxidase (GOx) or lactate oxidase (LOx)) and HRP. The polymerization of ETE-COONa was mediated by the ROx–HRP enzyme cascade. In this process, the ROx enzymes consumed native metabolites (lactate or glucose) within the tissue, generating $H_2O_2$ locally. This $H_2O_2$, in turn, acted as the oxidizing agent for the enzymatic polymerization of ETE-COONa, facilitated by HRP. The carboxylate groups were also used to covalently bond the resulting polymers locally to the gel. This gel-based polymerization procedure was performed in the brain, fin and heart of living zebrafish, as well as within living leeches and isolated mammalian muscle tissues, showing the broad applicability of this approach.

Notably, the formation of these gel-based electrodes was determined by the diffusion and chemical kinetics of the injected reactants within tissues, imposing constraints on the size and scalability of the electrodes. In the context of chronic in vivo applications involving the injection of monomer solutions, it is crucial to conduct systematic biocompatibility tests, including measures of potential inflammatory responses to reactants and particles. In addition, nanoparticles injected into the brain exhibit clearance half-lives of several days[62], although the kinetics and mechanisms responsible for clearing in situ-synthesized polymers remain unknown.

## Wound monitoring and therapy

Within a living organism, tissue injury is often accompanied by an elevated level of ROS. These ROS molecules can facilitate oxidative polymerization at the site of the injury, thereby enabling the potential for monitoring or facilitating wound healing[63–65]. For example, in situ polymerization of aniline derivative in hydrogel could be used for real-time monitoring and inhibition of wound bacterial infection, leveraging the overexpressed $H_2O_2$ in the infected wound (Fig. 4d)[63]. An aniline dimer derivative, *N*-(3-sulfopropyl) *p*-aminodiphenylamine (SPA), was combined with HRP and pre-loaded into a calcium alginate hydrogel. Once applied to an infected wound, an observable gradual shift in colour and near-infrared (NIR) absorption occurred within the hydrogel, indicating the synthesis of polySPA (PSPA) polymers. These polymers served as indicators for ongoing monitoring of infected wounds, both visually and via photoacoustic imaging. NIR laser illumination of the PSPA hydrogel substantially increased the wound temperature, which effectively inhibited the bacteria and promoted healing. The same reaction was conducted within tumours that exhibited an excessive expression of $H_2O_2$, which also allowed for photoacoustic monitoring and photothermal inhibition of tumours[64]. Moreover, the in situ production of conductive polymers enhanced the signal transmission of injured nerves and facilitated nerve regeneration[65]. At the location of a crush injury in the sciatic nerve, the aniline monomer underwent oxidation and subsequently formed PANI microvesicles. This synthesized PANI material contributed to electrical conduction within the injured nerve during the initial phase and was eventually cleared via lymphatic capillaries, thus preventing chronic inflammation. Despite the promise of this approach, it is essential to assess

whether the consumption of $H_2O_2$ (ref. 66) during polymerization reactions or the presence of exogenous polymers might slow down the natural healing process.

## Future perspectives

The emerging field of cell-based in situ polymerization offers a paradigm-shifting approach to crafting functional materials within living systems. By harnessing endogenous cellular environments and exogenous reactants and stimuli, this technique opens unprecedented avenues for tailoring polymer properties, achieving precise spatial control, and seamlessly integrating synthetic materials with biological entities. In this Review we have summarized the latest developments of polymerization techniques aimed at generating abiotic polymers within living cells and their diverse biomedical applications. These applications range from cancer therapy, bioimaging and the modulation of cell activity to maintaining cellular viability, fabricating electronic plants, developing neural interfaces and monitoring wound healing. Despite considerable progress in this field, many unexplored avenues hold the potential to broaden the scope of reactions across diverse organisms, enable better characterization and localization, and facilitate further biomedical advances and clinical translations.

Many other organic chemical reactions can be modified to integrate into living systems. This adaptation involves the incorporation of novel monomers, catalysts, initiators and polymerization methodologies, possibly in a cell-specific manner controlled by genetic targeting approaches[47]. In addition, bacteria can withstand various external agents and uniquely enable certain reaction conditions. For example, *S. oneidensis* could facilitate polymerization reactions that are sensitive to oxygen by depleting dissolved oxygen through aerobic respiration[67]. In comparison, such reactions tend to be cytotoxic to mammalian cells. To broaden biomedical applications in mammalian cells, it is essential to develop synthesis approaches that align well with physiological pH and oxygen levels, without disrupting native cellular activities.

Quantitative characterization is routinely performed for polymerization reactions outside a biological context. However, evaluating these reactions within the intricate cellular environment remains a challenge. For instance, in oxidative polymerization reactions catalysed by redox enzymes, enzyme expression levels and redox species concentrations can be measured using western blotting and fluorescent imaging, respectively. The polymers themselves, including non-oxidative-polymerization polymers, can also be fluorescently detected by co-polymerization with small-molecule fluorophores. The synthesized polymers can be isolated and characterized with NMR, mass spectrometry and gel permeation chromatography to monitor the polymer structure, molecular weight and polydispersity, and reaction yield. In addition, in vivo synthesis of abiotic polymers requires targeting of reactants and catalysts to specific organs, cell types and subcellular regions. This could be controlled either by native biochemical cues or well-established genetic engineering approaches. In this regard, the prospect of extending the genetically encoded bacterial biopolymer synthesis[68,69] to mammalian systems holds considerable promise.

Looking ahead, the potential biomedical applications are broad and promising. Fields such as bioelectronics and neurotechnology can benefit from the creation of functional polymers that interface seamlessly with biological systems, enabling advancements in devices and implants. Biosensing applications could be enabled through the integration of polymers that respond to specific biological cues, facilitating real-time diagnostics. The realm of regenerative medicine could also benefit from cell-based polymerization through the creation of synthetic scaffolds as artificial ECM, which could enable guided differentiation, cell encapsulation and protection, and tissue repair. Future integration into clinical contexts demands rigorous testing protocols to assess the effects of polymerization reactions on treated cells and their surrounding tissues over extended periods. Longitudinal studies are essential to observe any potential adverse reactions, unintended immune responses, tissue retention or other systemic effects that might arise from the introduction of abiotic synthetic polymers into the body.

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## Author contributions

A.Z., K.D. and Z.B. wrote the manuscript. S.Z. and J.T. contributed to the discussions and revisions.

## Competing interests

The authors declare no competing interests.

## Additional information

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