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Biological, Biomolecular, and Bio-inspired Strategies for Detection, Extraction, and Separations of Lanthanides and Actinides

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Synopsis: This review surveys the methods and current challenges for use of cells and biomolecules for harvesting f-block elements, emphasizing how the recent characterization of lanthanide-utilizing organisms may be translated into more effective extraction, separation, and sensing of these valuable elements.

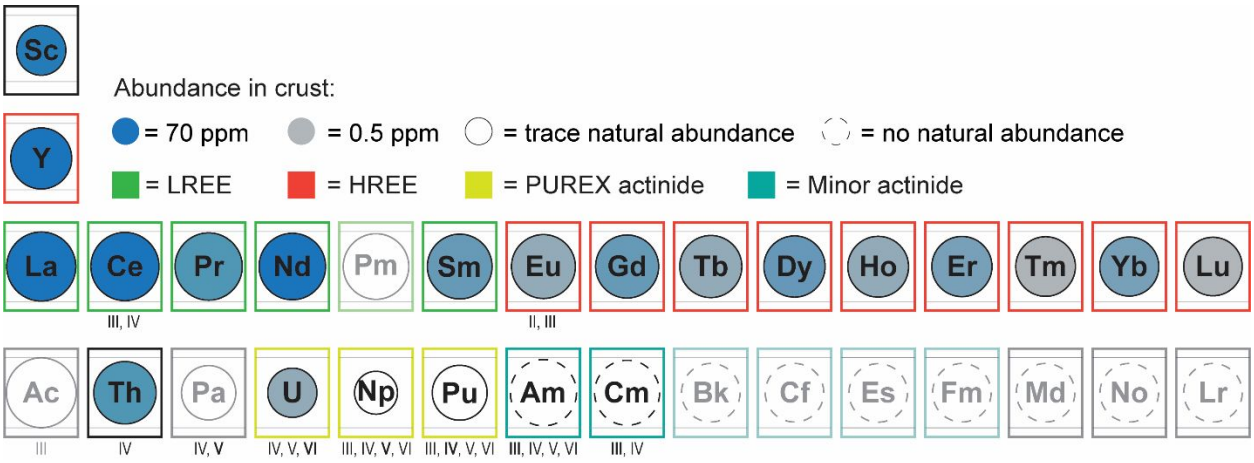
Abstract:

Lanthanides and actinides are elements of ever-increasing technological importance in the modern world. However, the similar chemical and physical properties within these groups make purification of individual elements a challenge. Current industrial standards for the extraction, separation, and purification of these metals from natural sources, recycled materials, and industrial wastes are inefficient, relying upon harsh conditions, repetitive steps, and ligands with only modest selectivity. Biological, biomolecular, and bio-inspired strategies towards improving these separations and making them more environmentally sustainable have been researched for many years; however, these methods often have insufficient selectivity for practical application. Recent developments in the understanding of how lanthanides are selectively acquired and used by certain bacteria offer the opportunity for a newer, more efficient take on these designs, as well as the possibility for fundamentally new designs and strategies. Herein, we review current cell-based and biomolecular (primarily small-molecule and protein-based) methods for detection, extraction, and separations of f-block elements. We discuss how the increasing knowledge regarding the selective recognition, uptake, trafficking, and storage of these elements in biological systems has informed and will continue to promote development of novel approaches to achieve these ends.

1. Introduction

The elements of the f-block of the periodic table – the lanthanide series (Ln, Z = 57-71) and actinide series (An, Z = 89-103) – are technologically important elements facing significant issues related to supply, separations, and recycling.[1–5] The Ln series together with scandium (Z=21) and yttrium (Z=39) comprise the rare earth elements (REEs), a grouping that is conventionally subdivided into light (LREEs: La – Sm/Eu) and heavy Lns (HREEs: Eu/Gd – Lu and Y) based on ionic radii (**Figure 1**). Many REEs are relatively common; the lightest REEs (Sc, Y, La, Ce, Pr, Nd) are found in the earth's crust average concentrations comparable to other well-known metals like copper, zinc, and lead, whereas HREEs (with the exception of Y) are generally found at much lower concentrations.[6] Among the An series, only Th and U are naturally occurring in significant abundance, similar to that of the HREEs;[4,7] however, the waste from nuclear reactors produces (in addition to the spent uranium) significant quantities of Pu, Np, Am, and Cm, the latter two being called "minor actinides."[8] All REEs, as well as actinium and the minor actinides, predominate in the +III oxidation state, whereas other actinides exhibit more variability in oxidation states.

Figure 1. Properties of REEs and actinides.[9,10] The elements are scaled by ionic radius (REE^{III}/An, CN = 9,[10] except for Sc^{III}, U^{VI}, Pu^{IV}, CN = 8, Np^{V}, CN = 6;[9] Bk-Lr, not scaled). The most stable oxidation states are in bold. The crustal abundances scale from blue (most abundant) to gray (least abundant) to white (trace natural abundance).[6] Elements depicted with a dashed circle are not naturally occurring and can only be prepared in a nuclear reactor or particle accelerator. Elements that are not discussed in this work are faded. Boxes are colored according to categorization.



The demand for REEs[11] has grown as a result of their unique electronic,[12] magnetic[13,14] metallurgical,[15] and medical[16–18] properties, which make them indispensable to myriad technologies. REEs can be found in display devices (Y, Tb), powerful magnets vital to electric motors and green energy (La, Dy, Nd), and medical imaging technology (Gd), to name a few.[5,19,20] Overall, the market value of these REE-containing technologies is on the order of $5 trillion.[21,22] Despite their unique uses, from a physicochemical perspective these elements are similar, because the 4f electrons have little impact on bonding.[23] As a result, not only do several REEs often co-occur in ores but the separation of one REE from another is a difficult chemical problem.[24] These challenges of co-occurrence and separation extend to the actinides: for example, the most abundant

source of thorium is the phosphate-based ore, monazite, which is also a major mineral containing several different lanthanides.[25] Similarly, separations of the lanthanides and minor actinides present in nuclear waste streams is complex.[3,4,26,27]

In general, the large-scale extraction and separations of both REEs and actinides utilize liquid-liquid extraction schemes (hydrometallurgy) using long-chain phosphoric or phosphonic acids and extraction into an organic phase, such as toluene.[5,12,24,28] Such ligands have high affinities for the highly charged REE cations and actinide ions, but they are relatively unselective for adjacent REEs, with only modest separations being possible between neighboring elements.[29] Consequently, high-purity production of individual REEs may require a solvent extraction step to be repeated dozens of times. The resulting purification processes consume large quantities of energy, acid, base, and solvent, and the waste generated from them is toxic and environmentally damaging.[30,31] In addition, the inefficiency of these approaches means that only highly enriched sources (~300 ppm REE content) can be utilized economically.[32] The majority of the known high-grade REE reserves are in the People's Republic of China, which currently dominates REE production.[5] As a result, the U.S. Department of Energy has identified several REEs as critical materials, with risk for supply interruptions in the short or medium term being especially high for Nd, Eu, Tb, Dy, and Y, with somewhat lower risks for La, Ce, and Pr.[33]

These challenges have motivated substantial research into novel methods to identify new mineral deposits;[5,34] to recycle REE-containing products in electronic waste (e-waste); and to develop improved extraction and separation processes to enable more sustainable use of existing sources as well as to tap non-traditional sources of REEs – including coal byproducts, acid mine drainage, and geothermal brines, which are currently too low-grade for economical REE recovery.[32,35,36] Meanwhile, detection methods used for identification and characterization of new sources and optimization of novel processes – with inductively coupled plasma mass spectrometry (ICP-MS) being the current standard – are sensitive but cumbersome, expensive, and time-intensive. Many creative approaches have been developed to address these challenges, from new chromatographic schemes[37] to novel ligands,[24] including small molecules[38–41], and supramolecular assemblies such as metal-organic frameworks (MOFs),[38,42] porous aromatic frameworks (PAFs),[43] and other functionalized materials.[44] Currently, most of these approaches are at the proof-of-principle stage on laboratory scale.

A greener, alternative approach to these challenging problems utilizes biological ligands. Investigations in this area date back decades but, as with the conventional industrial ligands, many of these processes are hindered by the heterogeneity and relative lack of selectivity exhibited by traditionally investigated bioligands[45] – bacterial cell surfaces, biopolymers, secreted acids, small molecules borrowed from other biological pathways (e.g. siderophores for iron uptake) or engineered small molecules or even proteins. The central motivation of this review is that the identification of REE-utilizing bacteria within the last decade,[46–49] and discovery of specific mechanisms for REE uptake, trafficking, and storage more recently,[50] demonstrate that biology has already discovered solutions to this problem that can be learned from and exploited. While relatively recent, the realization that lanthanides are used by certain biological systems should not be surprising because these metals are relatively abundant and have useful chemical properties (high Lewis acidity, uniquely high coordination numbers).[50] Since a recent review on this subject, focused on cell-based approaches,[51] many of the molecular details regarding lanthanide uptake and trafficking have been clarified and are beginning to be applied, allowing for analysis of the field from a chemical perspective. Biochemical characterization of these pathways and molecules may yield more efficient cell-based methods as well as more selective, effective, and modular molecular

approaches that can function under relatively mild conditions. Furthermore, due to similarities in coordination chemistry between Ln and many An ions,[3,10,52–54] many of these strategies may be extendable to actinides.

This review summarizes the state-of-the-art, major themes, and emerging opportunities regarding biologically based approaches for REE and An extraction, separations, and sensing. While the eventual viable solutions will have to balance a number of considerations, including economics, scalability, and adoption of new technologies,[55,56] here we focus on the fundamental chemical and biological principles underlying these processes. First, we introduce properties of the lanthanides and actinides and traditional processes for accessing them. Second, we summarize the relevant biology and biochemistry of these elements. Third, we review the diverse ways in which organisms and bio-derived molecules have been used for metal extraction, separation, and sensing applications. Finally, we discuss key, chemical advantages associated with using biological ligands (effectiveness, fast kinetics, facile re-engineering, mild conditions) and how emerging understanding of REE-utilizing organisms might be leveraged for myriad technological applications.

2. Rare earths and actinides: Occurrence and properties relevant to extraction and separation processes

2.1. Rare earth elements

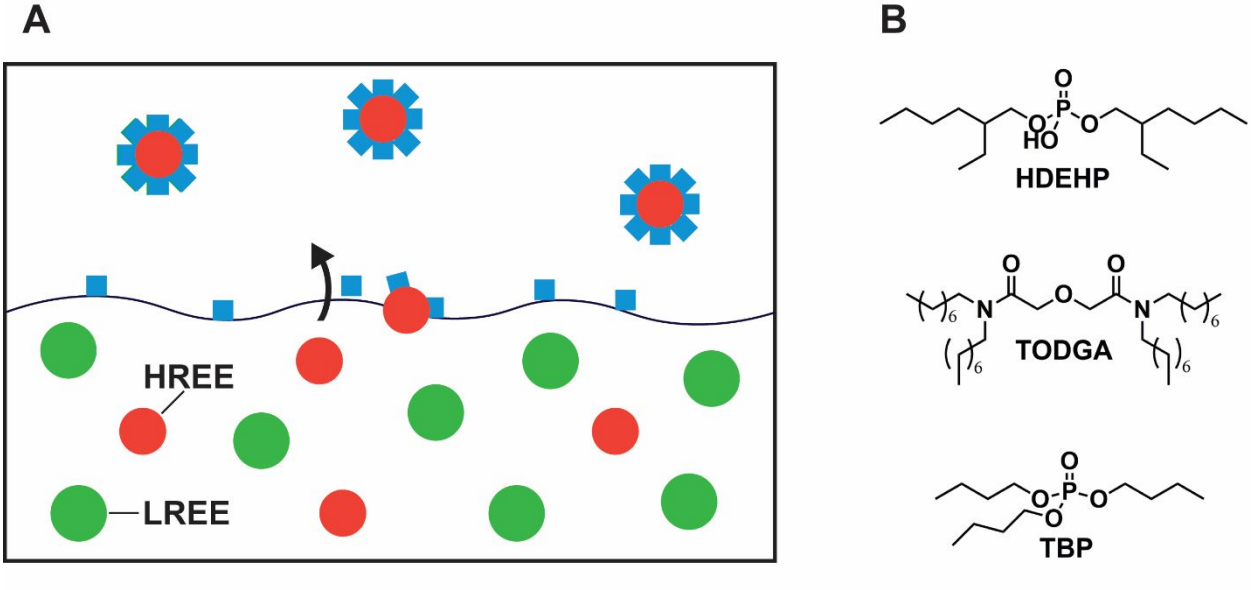
The central chemical challenges associated with selective detection, extraction, and separation of REEs are encoded in the names of these elements. First, they commonly co-occur in Nature: seven HREEs were discovered from the same deposit near the town of Ytterby, Sweden (yttrium, terbium, erbium, and ytterbium, as well as gadolinium, holmium, and thulium).[57] Second, separations of one REE from another are difficult: lanthanum (Greek *lanthanein*, to lie hidden) was discovered as an impurity in cerium; praseodymium and neodymium (the "green" and "new" "twins") were initially thought to be a single element.[58]

These challenges arise from the physicochemical similarities between the REEs, which have been reviewed.[58–60] REEs exist predominantly as hard, trivalent cations in solution chemistry and form stable, insoluble complexes with hard ligands, including common anions like phosphate[61] ($K_{sp} \sim 10^{-30}$) and hydroxide. The unique properties of the 4f electrons, which give rise to the valuable magnetic[14] and optical[62] properties of the lanthanides, also lead to the physicochemical similarities of the Ln^{III} ions. The 4f orbitals have radial probability distributions nearer to the nucleus than the 6s or 5p sublevels. Consequently, 4f electrons are poorly shielded from the nuclear charge, increasing from left to right across the series; as a result, ionic radii decrease with increasing atomic number (the lanthanide contraction).[23] This decrease in ionic radius is coupled with an increase in Lewis acidity. The ionic radii of Ln^{III} ions range from ~1.2 Å (La^{III}) to ~1.0 Å (Lu^{III}) for a coordination number (CN) of 9 (**Figure 1**); REEs exhibit high coordination numbers (8-12), especially for the LREEs. The buried 4f electrons do not participate significantly in interactions with ligands, and therefore bonding is predominantly ionic, resulting in sterically driven ligand coordination and chemical similarity of these elements, complicating separations.

The primary REE ores are bastnäsite, a fluorocarbonate mineral enriched for LREEs, monazite, a phosphate mineral also enriched in LREEs**,** and xenotime, a phosphate mineral rich in HREEs**.**[15] Suitable ores are often >10% rare earth oxides (REO), but must be refined (beneficiated) to 60-70% REO content before further processing. Refinement processes begin with liberation of REEs from ore solids. Strong acids can be used to leach REEs directly from their host ore matrices,

or various chemical and physical processes, such as treatment with sodium hydroxide or roasting, can be used first to decompose the lattice structure containing REEs in order to reduce the acid consumption of this initial step.[5] Individual REEs are then separated from one another using redox and hydrometallurgical processes.[5,12] Cerium and europium are unique among REEs for their ability to access non-trivalent oxidation states under relatively mild conditions. Ce^{III} can be oxidized to Ce^{IV} by roasting of concentrated REO whereas Eu^{III} can be reduced to Eu^{II}, allowing for efficient separation of these REEs from the rest.[5] The remaining mixture of REEs is separated via solvent extraction using various ligands[5,24] that drive phase separation (**Figure 2A**).

Figure 2. (A) Model for liquid-liquid phase separation of REEs based on ionic radius. (B) Ligands commonly applied in liquid-liquid phase separation of REEs/Ans.[3,5]



Extractants, such as alkyl phosphoric acids, are used to partition REEs to the organic phase, which is usually a hydrocarbon like toluene or kerosene.[4] Many examples of such extractants exist; the most commonly used are di(2-ethylhexyl) phosphoric acid (HDEHP) and *N,N,N',N'*-tetraoctyl diglycolamide (TODGA) (**Figure 2B**).[5,63] In accordance with the increasing Lewis acidity of the Ln^{III} ions across the series, these ligands exhibit increasing affinity, driving the selective leaching of heavier REEs to the organic phase. For an individual extraction step, the separation factor, which is given by the product of the molar enrichment of one element over the other in one phase and the analogous enrichment factor of the other phase, is small – averaging 2.5 for adjacent Ln^{III} ions across the series.[29] As a result, repeated extraction steps are necessary to achieve high purities of individual lanthanides. For example, the AS Megon process for producing high-purity yttrium oxide (99.999%) involves more than 90 stages of stripping, scrubbing, and extraction.[5,12,28] Although inefficient, these processes remain the industrial standard to due to relative cost efficiency and scalability. In accordance with the general trend of decreasing crustal abundance across the Ln series, the current prices for REOs (99.5% minimum) increase from ~$2/kg for La_2O_3 and Ce_2O_3, to $45/kg for Nd_2O_3, to ~$500 for Tb_2O_3 and Dy_2O_3.[25] Scandium, which co-occurs in minerals with other REEs at relatively low concentrations is more expensive: $3900/kg for 99.99% Sc_2O_3.[64]

The economic and technical difficulties of such methods, their environmental impact, and the continually increasing industrial demand for REEs have expanded interest in technologies capable of efficiently extracting REEs from low-grade feedstocks and common industrial wastes. REEs appear at low but significant concentrations in various common industrial waste products: mine effluent, mine tailings, coal fly ash, red mud, and e-waste.[65–68] Total REE content varies among these sources; for example, coal fly ash contains ~450 mg kg^{-1} total REE[22] whereas red mud may contain up to 1000 mg kg^{-1}.[66] However, these feedstocks also typically contain a large variety of metal contaminants that complicate the application of current extraction and separation methods. Therefore, new approaches must be developed if these alternative feedstocks are to become viable sources of REEs.

2.2. Actinides

The actinide series comprises solely unstable radionuclides, with only longer-lived thorium and uranium isotopes having appreciable abundances in the earth's crust (8.1 and 2.3 ppm, respectively), similar to the HREEs.[23] Uranium ores such as pitchblende contain uranium in the +IV and +VI oxidation states in variable quantities, but uranium is also found in significant concentrations in the oceans (3.2 ppb) due to the solubility of carbonate complexes of uranyl (UO_2^{2+}).[7,69] Th and U isotopes decay to mixtures of unstable radionuclides which include the other actinides; this process results in negligible amounts of naturally occurring actinide decay products.[23] Whereas large ionic radii and coordination numbers are shared by both REE and An series,[51] lighter actinides can access multiple oxidation states, facilitating separations.[70]

The primary consumer of actinides is the energy industry; in 2019, nuclear reactors accounted for about 10% of total global energy production,[71] generating 10,000 metric tons of heavy metal waste per year in the United States alone. This waste is predominantly uranium but also contains roughly 4-5% assorted fission products (all elements from Ge to Ba, plus La-Er), 1% Pu, and about 0.1% mixed actinides.[3,4,8] Long-term storage of raw nuclear waste is challenging due to the natural decay of fissile materials, necessitating reprocessing and maintenance.[3] Furthermore, spent nuclear fuel contains a valuable mixture of scarce, technologically important actinides. For example, americium is ~50-times more expensive than gold ($1,500 per g) although its only widespread use is in smoke detectors, curium is used as and α-particle emitter for x-ray spectrometry in space exploration,[72] late actinides can be used to transmute super-heavy transactinide elements,[73] whereas others like neptunium can be transmuted and recycled as fissile material.[74] Uranium and plutonium can be recovered for recycling back into the nuclear fuel cycle using the plutonium uranium extraction (PUREX) process.[3] In this process, uranium and plutonium are partitioned from the bulk of fission products, to an organic phase, using the tri-*n*-butyl phosphate (TBP) ligand (**Figure 2B**). Taking advantage of the higher reduction potential of plutonyl versus uranyl, the Pu^{VI} in the actinyl-TBP complex is selectively reduced to Pu^{III}, allowing for back extraction to the aqueous phase. This process can also be modified to extract neptunium.[75]

While the efficient separation of U, Pu, and Np from the remaining fission products is well established, the separation of the latter is more difficult. In particular, this remainder contains a mixture of minor actinides (including Am and Cm) as well as several REEs (La-Er, Y). As with the lanthanides, the +III oxidation state of Am and Cm predominates, and their ionic radii are similar to each other and to Nd^{III},[10] complicating separations.[3] Softer ligands have been applied to preferentially bind to the more covalently bonding actinides over the more ionic-bonding lanthanides.[27,76] Despite these differences, the separation of minor actinides from lanthanides and from each other remains a challenging problem.

3. Biological roles of rare earths and actinides

3.1. Non-specific roles of lanthanides in biology

Non-specific interactions between REEs and biological systems for extraction purposes have been explored for decades. The high concentration of phosphates (phospholipids), hydroxyl groups from sugars and biopolymers like chitin and cellulose, and carboxylates from alginate, make cell surfaces and extracellular biopolymers excellent platforms for REE concentration via adsorption,[45,77] albeit with specificity primarily deriving from the higher charge of REEs compared to other metal ions.

In addition to adsorption to the organism's surface, REE absorption has also been described extensively, especially in plants (reviewed in refs. 50 and 78). The chemical basis for these studies is the shared hard Lewis acid properties of trivalent REEs to metal ions ubiquitous in biology, Mg^{II} and Ca^{II}, shared preferences for biological ligands like carboxylates, and the similar ionic radii of Ca^{II} and LREEs (1.12 Å for Ca^{II}, CN = 8, similar to Pr^{III}). In theory, the redox-inactive nature of most REEs under physiological conditions and robust Lewis acidity could make them suitable substitutes for Ca^{II} and Mg^{II}, although more subtle differences (e.g. coordination geometries, affinities, lability, insolubility) may also make them inhibitors and therefore toxic to the cell.[58,78–80] Modest concentrations of LREEs have been used for decades in China increase the yield of some crops.[81] In laboratory-based experiments, nutrient solution (0.05-0.75 mg REE L^{-1}) increases crop growth, but higher concentrations are detrimental.[81] Changes in chlorophyll production[82,83] have also been reported, particularly in magnesium-deficient soils. Elucidation of the mechanisms by which REE effect plants is still in its infancy.[84] However, the discovery that plant-associated bacteria (see 3.2) utilize REEs suggests that the effects on plant growth may also reflect plant-microbiome interactions.

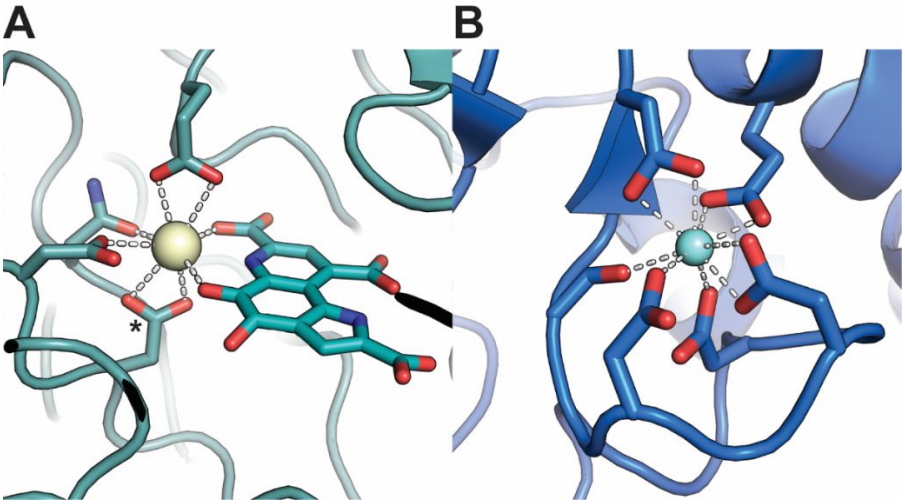
3.2. Specific utilization of lanthanides in bacteria

The paradigm that the biological roles of REEs were solely non-specific and often toxic was overturned in 2011, with the discovery that addition of La^{III} and Ce^{III} to culture media induced methanol oxidation activity in methylotrophic bacteria, an effect linked to incorporation of these ions into XoxF, a pyrroloquinoline quinone (PQQ)-dependent methanol dehydrogenase (MDH) of previously unknown function.[46–48] The essential role of REEs in biology was confirmed in 2014, with the discovery of a thermophilic bacterium (*Methylacidiphilum fumariolicum* SolV) that requires REEs for growth, again linked to XoxF.[49] Previously, methylotrophic bacteria were only known to use a Ca- and PQQ-dependent MDH, MxaFI.[85] The active sites of XoxF and MxaFI are almost identical, with the exception of an additional carboxylate ligand in the case of the Ln-dependent MDH (asterisk in **Figure 3A**). Homologous lanthanide-dependent methanol dehydrogenases and other PQQ-dependent alcohol dehydrogenases were characterized in multiple other methylotrophic bacteria[86–88] and even in non-methylotrophic soil-dwelling bacteria,[89] clarifying that Ln utilization is widespread in the environment, including in soil, associated with plants, and in the ocean.[90–92]

These discoveries galvanized biochemical inquiry into Ln-related pathways, especially into mechanisms of uptake, sensing, and trafficking of lanthanides – all of which might open new avenues for biological approaches for REE harvesting and sensing. The first lanthanoprotein other than an alcohol dehydrogenase to be characterized, and the first selective biological chelator of lanthanides, was lanmodulin (LanM), from *Methylorubrum extorquens* AM1, in 2018.[93,94] LanM is a small, 12-kDa protein that undergoes a conformational change from a disordered state to a

folded state, highly selectively, in response to REEs. LanM contains 3 high-affinity (picomolar) metal-binding sites and 1 low-affinity site (micromolar) (**Figure 3B**). These sites are classified as "EF-hands," ~29-residue helix-loop-helix motifs that include a 12-residue metal binding loop with characteristic spacing of carboxylate residues, which are found in myriad calcium-binding proteins such as the eukaryotic calcium sensor, calmodulin.[95,96] Typical EF hands tend to bind Ln^{III} with slightly (10-100-fold, in the nanomolar to micromolar range) higher affinity than their native metal ion, Ca^{II}, as expected for a trivalent vs. divalent ion.[97] However, LanM displays unprecedented affinity (picomolar at 3 of its 4 sites) and selectivity (10^8-fold) for REEs over other metal ions, including Ca^{II}.[93,98,99] Unlike most REE chelators, which favor binding of the more Lewis-acidic HREEs, LanM appears to have relatively modest selectivity across the lanthanide series, although coupling of metal binding and protein conformational change is optimal for only the LREEs.[93,98,99] Several aspects of the metal-binding site and the overall protein architecture have been shown to contribute to this unusual metal selectivity pattern, serving to establish key principles of selective recognition of lanthanides in biology;[93,94] however, more work remains to fully understand the mechanism of LanM's extreme REE selectivity as well as the protein's physiological function.

Figure 3. Structurally characterized biological REE-binding sites. (A) Active site of the Ln-dependent MDH, XoxF, from *M. fumariolicum* SolV, modeled with Ce^{III}, with the PQQ cofactor (cyan) and metal ligands (blue-gray) shown in sticks.[49] The extra carboxylate ligand (relative to MxaF) is depicted with an asterisk. (B) NMR solution structure of Y^{III}-bound LanM, showing the model of the REE-binding EF-hand 3.[94]



The *lanM* gene in *M. extorquens* AM1 is part of a 10-gene cluster that appeared to constitute a lanthanide uptake system based on the presence of 4 genes equivalent to machinery commonly associated with Fe^{III} uptake via secreted small molecules called siderophores.[98,100,101] The gene cluster also contains several genes of unknown function, one of which encodes another Ln-selective protein, which uses a metal-binding site distinct from an EF hand.[98] This uptake machinery was discovered in several organisms roughly contemporaneously[98,100,102,103] and evidence was reported in *M. extorquens* for the existence of a secreted chelator selective for early Ln^{III} ions, a lanthanide metallophore,[98] or lanthanophore for short.[104] Similar mechanisms of uptake likely exist in other Ln-utilizing bacteria.[92,105]

LanM was adapted into a fluorescent, Förster resonance energy transfer (FRET)-based sensor for REEs which conserved the useful metal-binding affinity and REE-selectivity observed

in the wild type protein, illustrating how biological strategies for REE-coordination can be directly translated into useful industrial and scientific tools (see also 5.1).[98] This sensor allowed demonstration that the same Ln^{III} ions that support robust Ln-dependent growth of *M. extorquens* (La-Nd) also are selectively taken up into the cytosol. Because all of the previously identified proteins involved in Ln utilization were periplasmic, it was unknown at the time what Ln-dependent functions exist in the cytosol, although they presumably would include other enzymes, regulatory systems, and/or metal storage. Indeed, recent work has also shown that, like many other biological metals (calcium, iron, copper, and zinc),[106,107] Lanthanides are also accumulated and stored in phosphate-containing granules in the cytosol.[103] The potential application of Ln-utilizing organisms;[51] Ln uptake, trafficking, and storage pathways inserted into other heterologous organisms; and proteins or small molecules used in cell-free systems[50] for biometallurgy will be discussed in more detail in sections 4 and 6.

The bacteria presently known to utilize REEs for specific purposes use only LREEs, with the ability to use various Ln falling off at different rates across the series (e.g., La and Ce in *Bradyrhizobium*,[46] La-Nd in *M. extorquens*,[98,100,108] and La-Gd in *M. fumariolicum*.[49]) The molecular origin of this preference for LREEs appears to derive from a combination of LREE-selective uptake mechanisms (a secreted lanthanophore),[98,100] redox matching between the Ln^{III}-PQQ cofactor in XoxF and its electron acceptor,[88,109] Ln^{III}-dependent stability of XoxF,[110] and potentially other as yet uncharacterized pathways. Organism-dependent differences between these factors may contribute to differences in the specific Lns that support growth. However, there are no reported examples to date of organisms that can efficiently utilize Ln past Gd, and even those that can use Sm, Eu, and Gd do so poorly.[49,89]

Because the HREEs are present at 10-100 times lower concentration on average in the earth's crust (with the exception of yttrium, which is similarly abundant as the LREEs),[6] and consequently tend to be more valuable, discovery of organisms that are able to selectively utilize some of the HREEs could be useful from a biometallurgical perspective.

3.3. Actinides

Actinides have no known specific biological roles. The interactions of actinides and biological systems from bacteria to humans has been recently reviewed.[7] Th and U are the only actinides that occur naturally in significant amounts, with abundances similar to those of the REEs.[6,7] Although the radioactivity of these elements may limit their utility for specific, essential biological functions, metal-reducing bacteria such as *Shewanella* can use uranium(VI) as an (extracellular) electron acceptor for respiration[111,112] and *Citrobacter* adsorbs large quantities of uranium.[113] Other bacteria, such as *Caulobacter crescentus*, exhibit pathways linked to uranium resistance,[114] and bacteria isolated from Pu-contaminated waste sites have adapted to the presence of actinides and can contribute to An redox cycling.[115]

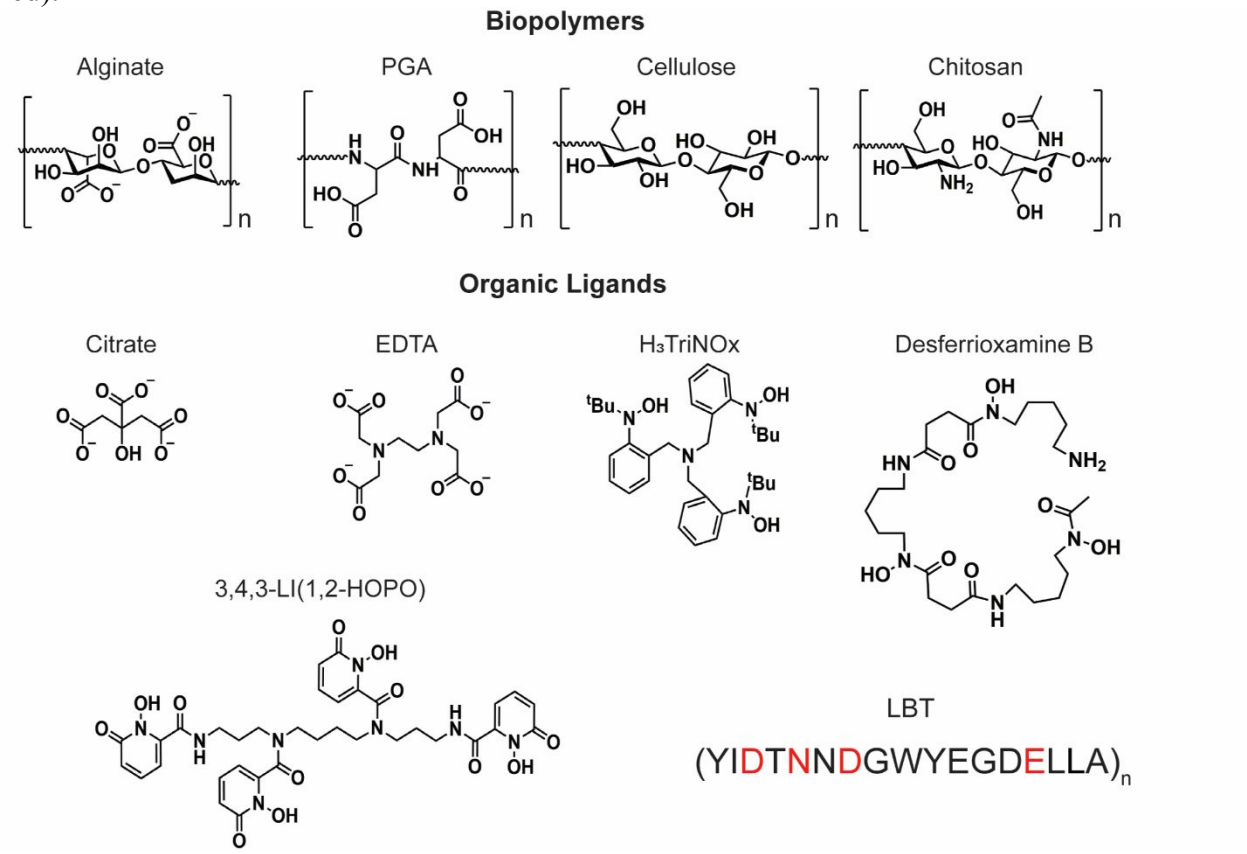
However, now that significant quantities of other actinides are present in the environment from anthropogenic sources, it is likely that a substantial bioinorganic chemistry of An ions exists. The coordination chemistry of Ln^{III} ions is similar to trivalent An ions, such as the minor actinides, with An^{III} complexes typically possessing slightly higher affinities than for the corresponding Ln^{III}.[10,70] The ionic radii of Am^{III} and Cm^{III} are most similar to Nd^{III}, and Bk^{III} and Cf^{III} most similar to Sm^{III}.[10] It is almost certain that these actinides would bind tightly to Ln-binding proteins like lanmodulin, enzymes like methanol dehydrogenase, and lanthanophores. In addition, because Nd^{III} is used by most of the Ln-utilizing bacteria studied so far, it is plausible, and even likely, that Am^{III} and Cm^{III} ions could be taken up by the organisms and activate PQQ-dependent alcohol

dehydrogenases, and possibly other yet-to-be discovered proteins in the lanthanome, in vivo. It may even be possible that tetravalent Ans (Th^{IV}, Pu^{IV}) can be used by these systems, given links between the speciation of these ions and that of Fe^{III} and Ca^{II} in humans,[7] as well as the already clear analogies between the coordination chemistry of Fe^{III} and Ca^{II} and REE uptake and trafficking pathways in bacteria.[50]

4. Biological methods for extraction and separation of f-block elements

Driven by their high positive charge, REEs and actinides form stable complexes with many anionic compounds commonly found in biological systems (phosphates, carboxylates, hydroxides), as well as widespread biopolymers (chitin, cellulose, alginate). These interactions have been explored for decades in an attempt to extract and/or separate these technologically valuable elements. In this section, we discuss the variety of ways that cells and biomolecules can be used to extract these metals, beginning with whole-cell approaches and transitioning to molecular approaches. We do not provide an exhaustive enumeration of all examples of each approach; we refer the reader to several reviews of various biological materials and their derivatives,[116] bacteria/fungi,[45,117,118] and plants[119] for more details. Instead, we provide representative examples and the insight that they give into the central challenge of achieving useful selectivity between these metals and against other common and strongly interacting metal ions.

Figure 4. Chemical structures of selected biopolymers, organic acids, and a hydroxamate siderophore (desferrioxamine B). Also depicted are biologically-inspired synthetic ligands H_3TriNOx[120] and 3,4,3-LI(1,2-HOPO)[70] and a single LBT unit (with metal-binding sidechains in red).[121]



4.1. Whole cell biosorption

Metal ions can be present in an environment in soluble or insoluble form. Cells may interact with metals via direct adsorption (biosorption), internalization, or mobilization with the help of lixiviants (liquids containing molecules capable of liberating metals from a solid feedstock). Because biosorption takes place on the cell exterior, it is a particularly attractive mechanism for metal extraction because rapid mass transfer is observed, within hours. Cell surfaces are ideal for metal adsorption because of their large surface area per unit weight.[117,122] However, adsorption capacities of unmodified biomass are typically low (these values on average range between 10-20 mg/g dry weight, although some numbers as high as 100 mg/g are reported[77,123]), as is the selectivity, due to the heterogeneity of the cell surface ligands. Nevertheless, functionalization can increase both of these characteristics (**Table 1**).[124,125] Optimal conditions are generally mild, with pHs for adsorption ranging between 3-6.[117,119] High pHs favor formation of insoluble metal hydroxides, while low pHs may protonate ligands, limiting binding. Intermediate pHs will protonate some of the potential cell ligands, offering some selectivity in metal binding.[126] Desorption, or removal of the metal from biomass, can be accomplished through the addition of excess ligand, such as citrate or ethylenediamine tetraacetic acid (EDTA) (**Figure 4**), to the mixture, or by lowering pH. Conditions such as pH, temperature, pulp density, biomass concentration, and incubation time can all be tuned to optimize adsorption efficiency and improveselectivity during desorption.[117] Unfortunately, however, selectivity is not always addressed in the literature when assessing new adsorbents.

Table 1. Representative examples of biological methods for REE and uranyl extraction

Name (Reference)	Metals	Adsorption capacity (mg g^{-1})	pH	Comments
S. cerevisiae[123,127]	Ln	~16-40	4	Limited, unselective cation adsorption; reuse not addressed
Phosphorylated *S. cerevisiae*[127]	Ln/Y	~100/59	4	Selective adsorption of Lns at pH 2, reuse not addressed
S. cerevisiae rim20Δ[123]	La	70	4	Selectivity and reuse not addressed
Chitosan[128]	Eu	48	3	Selectivity and reuse not addressed
Phosphorylated graphene oxide-chitosan[129]	U	780	5	Selective vs. divalent and trivalent cations; desorption requires concentrated acid; reuse not addressed
Phosphorylated chitosan carboxymethyl cellulose[130]	U	980	5	Enhanced selectivity vs. divalent and trivalent cations; desorption and reuse not addressed
Chitosan nanoparticles[131]	Eu	120	3-7	Selectivity and reuse not addressed
Amidoxime-functionalized magnetic chitosan[132]	Eu/U	380/360	4-5	Limited selectivity vs. heavy metals; efficient for ≥5 cycles
Cellulose[133]	Er	47	5	Selectivity not addressed; loss of ~7% efficiency over 5 cycles
Thiourea-functionalized cellulose[133,134]	Nd/Eu	27/73	N/A	Selectivity not addressed; loss of ~10% efficiency over 5 cycles[133]
Calcium alginate gel beads[135]	Nd	200	3.5	Selective vs. most common cations ($R_{Nd/M}$>20) except Fe^{III}, Cr^{III}, Al^{III}, Cu^{II}; Stable for 8 cycles

Sodium γ-PGA[136]	Nd	310	3	Unselective vs. Cu^{II}; reusability not addressed
Calcium alginate PGA hybrid gel[135]	Nd	240	3.5	Highly selective vs. most common cations ($R_{Nd/M}$>50) except Fe^{III}, Cr^{III}, Al^{III}, Cu^{II}; Stable for 8 cycles
Caulobacter crescentus LBT[137]	Ln	9	6	Preferential binding of HREEs; stable for 3 cycles; requires addition of Ca^{II}
Curli-LBT[138]	Ln	47	6-7	Mildly selective for HREEs; loss of 50% overall sorption in presence of mixed metals. Effective after 3 cycles.
Amidoxime functionalized *Aspergillus niger*[139,140]	U	620	5	Preferential binding of uranyl over common cations; 87% efficiency after 8 cycles
Dried green algae, *Parachlorella*[141]	La	6	7	Selective against cations found in Vietnamese clay minerals, reusability not discussed
Lanmodulin (LanM)[99]	Ln	40[1]	3-7	Quantitative and highly selective total REE purification, reusability for at least 7 cycles
Spidroin-based super uranyl-binding protein fiber (SSUP)[142]	U	12	6	Highly selective vs. common cations; 69% adsorption capacity after 10 cycles

[1] For protein alone (not immobilized)

Many different biological samples, from algae to grapefruit peels, have been examined for their potential utility in biosorption of REEs and actinides,[116,143–146] to concentrate metals from low-grade feedstocks, remediate industrial waste, or liberate metals from solid e-wastes such as spent phosphors.[66,128,147] Most organisms display a net negative charge to their external environment, making both whole-cell and membranous extracts useful for biosorption of metal ions. Although typically non-specific, these ubiquitous interactions may be useful as a first pass in bioremediation of contaminated wastes or concentration of valuable metals from low-grade feedstocks.[143] Biosorbents confer a number of intrinsic advantages, such as compatibility with mild conditions, efficiency in dilute effluents, fast kinetics, and being environmentally benign.[119,124,148]

Algae are a well-studied, common, and diverse group of aquatic organisms with a demonstrated capacity for biosorption of heavy metals. The algal cell wall is primarily composed of the commonly occurring biological polysaccharides cellulose and alginate, which can constitute as much as 60% of the dry mass of brown algae.[149] These molecules are rich in carboxylate and hydroxyl groups that are ideal for REE/An adsorption, and are readily functionalized (**Figure 4**).[150] Many different types of algal biomass as well as chemically modified derivatives have been characterized for biosorption of REEs/actinides (**Table 1**).[66,125,141,151–154] Various bacteria and fungi, as well as their extracts, have also been evaluated.[45,117,124] Industrially feasible REE harvesting by baker's yeast, *Saccharomyces cerevisiae,* is promising because of yeast's amenability to large scale production and its well understood physiology. Whereas the adsorption capacity of wild-type *S. cerevisiae* is relatively low (16 mg/g, **Table 1**), total REE adsorption capacity is increased significantly in a mutant with enhanced surface-display of negatively charged moieties (rim20Δ),[123] or by chemical functionalization with metal-ligands such as phosphate.[127] The simplicity of these ligands limits the potential for metal selectivity in these systems, likely to that which is achievable by weakly acidic cation exchange resins.[155] The immobilization of biomass to a solid phase like activated alumina,[156] cellulose,[157] or chitosan derivatives[147] can potentially increase the efficiency of biosorption and prevent degradation of the biosorbent during desorption (often accomplished using 0.1 M HCl), allowing for reuse.[158] However, these matrix materials also bind metals,[156,157] contributing significantly to the final sorbent capacity. The

contributions of matrix materials to metal selectivity and capacity have not been fully explored in many cases.

Alternative strategies apply organisms resistant to environmental concentrations of REEs that are toxic for most systems. For example, *Thermus scotoductus* SA-01, a bacterium isolated from a gold mine, is resistant to up to 1 mM Eu^{III}, enabling nearly quantitative removal of 0.5 mM Eu^{III} within 9 h.[159] The accessibility of the Eu(III/II) redox couple also allows for bioreduction, by a *Clostridium* strain found in REE-contaminated waters.[160] In *Myxococcus xanthus*, La^{III} induces production of external polymeric substances (EPS), polyanionic organic substances that contain a number of metal ligands such as carboxylates, phosphates, amino, amide, and hydroxyl groups, leading to metal precipitation.[161] These extracellular biopolymers interact with the La^{III} ions and localize them to the cell wall.[45,77] Similar approaches also apply to actinides. Biosorption, intracellular accumulation, precipitation, and redox transformation have all been reported.[112,161–164] Interactions between bacterial EPS and actinide ions are of particular importance because the EPS facilitates metal reduction, reducing solubility and bioavailability and therefore mitigating environmental impact. Incubation of EPS of *Pseudomonas* sp. strain EPS-1W with Pu^{V} resulted in rapid reduction of the metal to insoluble Pu^{IV},[115] while stimulation of EPS production and reduction of U^{VI} to insoluble U^{IV} by *Shewanella oneidensis* MR-1 has also been reported.[165]

Although most of the above work focuses on extraction rather than separation, recent work using the Gram-negative bacterium, *Roseobacter* sp. AzwK-3b, suggests that separations between HREEs and LREEs may be possible even using biosorption.[126] Taking advantage of the fact that the more Lewis-acidic HREEs require lower pHs to desorb from the cell surface, incubation of cells with an equal mixture of Ln^{III} ions at pH 2.5 led to progressive enrichment of Yb and Lu to ~50% of total REEs after 2 cycles. While a promising and organic solvent-free approach, multiple adsorption/desorption cycles are still required, as with currently used separation technologies.

4.2. Biopolymers

Sorbent biopolymers such as cellulose, chitin/chitosan, and alginate exhibit modest capacities and minimal selectivity for REEs and actinides (**Table 1**). However, the backbone of these polymers is readily functionalized, and incorporation of various biomass or ion-exchangers has be used to increase their viability for REE/An sorption.[133] The repeating monomeric units of cellulose [β-(1→4)-D-glucose] present three hydroxyl groups, for easy functionalization or metal ligation.[130,133,134,157] Chitin [poly(β-(1→4)-*N*-acetyl-D-glucosamine)], found in the exoskeleton of arthropods and the cell wall of yeast or fungi,[166] as well as its partially deacetylated derivative, chitosan, interact with cations through their acetamido and hydroxyl groups.[124] Deacetylation of chitin to form chitosan increases aqueous solubility of the polymer and also enables metal coordination[166] and functionalization via the free amines, producing derivatives with improved sorbent properties and potential for crosslinking to other molecules or to other types of biomass.[127,128,133]

Chitosan derivatives with enhanced sorption properties include those functionalized with chelator [e.g., EDTA, diethylenetriamine pentaacetic acid (DTPA)],[167] titanium oxide,[168] acryloylthiourea[169] and phosphonic acid.[170] Amidoxime-functionalized magnetic chitosan is stable for multiple cycles and has been used for removal of U and Eu from aqueous samples, although its selectivity against common heavy metals was limited (**Table 1**).[132] Phosphorylated chitosan covalently linked to a graphene oxide framework quickly (<10 min) and selectively removes up to 90% of uranyl from solution at pH 5.[129] Similarly, a phosphorylated chitosan/cellulose polymer selectively adsorbs uranyl at pH 5.[130]

Alginate, the primary constituent of the algal cell wall, is a linear copolymer of randomly arranged 1,4-linked β-D-mannuronic and R-L-guluronic acids, rich in carboxylate and hydroxyl moieties.[135] Alginate is also readily functionalized; alginate gels and hydrogels have been shown to be resilient and effective at removing REEs and U from aqueous solution.[171,172] For example, a calcium-alginate-polyglutamic acid hybrid gel maintained 240 mg/g Nd adsorption capacity for up to eight adsorption/desorption cycles (**Table 1**).[135] In an alternative approach, silica-doped alginate beads showed remarkable mechanical strength, maintaining optimum Nd adsorption capacity (140 mg/g) through twelve adsorption/desorption cycles.[173] Whereas these polymers exhibit good selectivity over most metal ions, other trivalent metals and Cu^{II} compete with REEs.

4.3. Small-molecule lixiviants

There are three approaches to lixiviation: acid leaching, base leaching, and chelator-based leaching.[118] Requirements for this step differ based on the physiochemical properties of the feedstock. Rare earth ores, like bastnäsite or monazite, typically necessitate harsh acidic or basic conditions to liberate the metal,[5] whereas the metals contained in recycled materials, like e-waste, are more chemically available but often embedded in a polymeric or ceramic matrix that must be ground to increase accessibility to lixiviants.[174,175] Biological molecules with potential utility as industrial lixiviants are commonly produced by myriad microorganisms.

4.3.1. Organic acids. Simple organic acids, such as citrate, oxalate and gluconate are commonly secreted by most microorganisms, in part to function in metal uptake.[176] These molecules are collectively known as exudates when they are the product of organismal secretion. Recent work has demonstrated the efficacy of using individual microorganisms or microbial communities, as well as filtered, exudate-containing media, for REE/An-leaching from low-grade feedstocks and industrial waste products.[137,174,177–180] Phosphate-solubilizing fungal strains have been shown to be effective at selectively removing REEs from monazite sands, a common REE ore which also contains Th.[179] Interestingly, the exudate-containing growth media from both of these examples outperformed abiotically prepared organic acid solutions, suggesting that the complexity of these systems is not fully understood.[179,181] Therefore, bacterial communities and biotically prepared mixtures of lixiviants may prove useful for accessing difficult feedstocks.

Some organisms appear to have adapted to the adversity of heavy metal contamination, and the toolbox employed by such organisms likely contain useful strategies for metal processing. For example, a *Penicillium tricolor* RM-10 strain isolated near a disposal site for red mud (waste from digestion of bauxite, which contains high REE, Th, and U content) was remarkably resilient to red mud toxicity, even at pulp densities as high as 10%. Increased secretion of citric and oxalic acids was observed in these conditions. This natural physiological response of *Penicillium tricolor* RM-10 to red mud leached up to 40% Th and 70% REE content.[177]

Nutrients used for biomass production constitute a major portion of the costs associated with bioleaching operations.[56,174] For example, glucose is the major expense in gluconic acid production by *Gluconobacter oxydans,* which has been used in leaching of REEs from industrial waste products like retorted phosphor powder (RPP) and spent FCC.[181] These costs can be minimized through efficient use of energy-rich agricultural waste products, such as corn stover, for biomass production.[174] The performance of this production method compared favorably with traditional approaches, leaching up to 25% of the REE content of FCC powder in under 24 h. The net profit of this design was at least five times greater than using traditional glucose sources demonstrating the economic feasibility of optimized, large-scale bioremediation.[174]

4.3.2. Metallophores

Metallophores are small molecules secreted by bacteria, fungi, and plants that are involved in selective metal ion uptake, and these molecules have been explored for hydrometallurgical purposes (**Figure 4**). Metallophores with high specificity for Fe^{III} (siderophores, the most extensively characterized class of these molecules),[101,182] copper (chalkophores including methanobactins),[183] zinc (including psuedopaline and staphylopine)[184] and more broad-spectrum metallophores, such as plant-secreted phytometallophores.[185,186] Lanthanophores are known to exist but their structures have not yet been reported.[98,100,102,103] The major metal-coordinating functions found in characterized metallophores are catecholate, carboxylate, and hydroxamate groups, although amine coordination occurs, and chalkophores employ sulfur, through thioamide or enethiol groups, for softer copper ions.[183,187] Some lanthanophores might reasonably contain phosphate since major REE minerals are phosphate based. The various coordination strategies employed by biology in metallophores has inspired development of various synthetic molecules with alternative, useful metal-binding tendencies (see ref. [188] for one such example).

Before it was fully appreciated that dedicated Ln-metallophores exist in biological systems, researchers suggested that siderophores play a non-specific role in bioaccumulation of REEs;[176,189] a similar crosstalk between iron and REE uptake may also occur in REE-utilizing bacteria.[190] The structural characteristics of known siderophores inspired the creation of important f-block chelators, especially the hydroxypyridonate (HOPO) and hydroxamate scaffolds. The HOPOs are a family of siderophore-inspired ligands whose interactions with REEs and Ans have been well explored.[16,52,54,191–198] One member of this family, 3,4,3-LI(1,2-HOPO) (343HOPO, **Figure 4**), preferentially binds tetravalent cations to an extent that allows for large separation factors ($S_{An/M}$ $>10^6$) between certain Ans (Pu, Bk) and trivalent cations (Ln^{III}, Ac^{III}, Am^{III}, Cm^{III}).[70] The thermodynamic preference of 343HOPO for tetravalent metals promotes oxidation of Bk^{III} to Bk^{IV}, allowing for efficient separation from Ln^{III} ions and Cf^{III}, with single-step separation factors ranging from 10^3-10^6 over a wide pH range.[70,199] Recently, the spermine backbone of 343HOPO was replaced by peptoid units, allowing for the efficient synthesis of complex ligands with mixed 1,2-HOPO and/or catecholamide moieties. A combinatorial library of tetrameric peptoids with these two possible metal-coordinating moieties showed enhanced affinity for Ln^{III}, demonstrating the potential for evolution of more diverse ligand architectures in order to tune selectivity.[200]

Hydroxamate-containing siderophores also serve as the basis for a group of synthetic ligands with the ability to perform REE separations. The tris(2-tert-butylhydroxy-aminato)benzylamine (TriNOx) family of ligands form stable complexes with REEs (**Figure 4**). These metal-ligand complexes preferentially dimerize when coordinating larger REEs. The differing solubilities of the dimers and monomers in benzene,[40] later adapted for a "greener" solvent toluene,[201] allows for efficient separations between REEs with sufficiently different ionic radii. Although the formation of mixed dimers is expected to complicate separations in more complex mixtures, binary REE mixtures showed promising results, for example a separation factor of 360 for the important Nd/Dy pair.[40] Further exploration and optimization of the original TriNOx scaffold allowed for enhanced separation factors through exploiting the inherent magnetic and redox properties of different Ln^{III}-TriNOx complexes.[1,40,41,120,201,202] These complexes highlight the potential value in exploiting cooperative metal binding in separations applications, exhibited by several other small molecule approaches[38,39] as well as in lanmodulin.[93]

In 2016 Martinez-Gomez and Skovran showed that *M. extorquens* is capable to taking up Nd^{III} from crushed NdFeB magnets.[51] Methylotrophs are advantageous organisms for this purpose

as only methanol is needed as a carbon source. At the time it was not known that a specific metallophore was involved in LREE uptake, and cellular toxicity of other metals in the magnet was a challenge. The more recent description of the lanthanophore uptake system suggests that cell-free lixiviant systems may be possible to avoid this toxicity; it is possible that a similar principle to solvent extraction processes may be applicable using these ligands, given typical architectures of metallophores and their receptor recognition mechanisms.[101]

4.4. Peptides and proteins

Peptides and proteins can form higher-order structures that impart more complex physiochemical behavior and selectivity than many small molecules, they are highly customizable, generally nontoxic, and biodegradable. A relatively simple example of a peptide-based REE extraction utilizes poly-γ-glutamate (γ-PGA), a biopolymer produced by *Bacillus* sp.. This polymer exhibited a 305 mg/g adsorption capacity for Nd^{III}, stable over many sorption/desorption cycles (**Table 1**).[136] However, co-adsorption of Cu^{II} indicates similar selectivity challenges to many of the previously described ligands. The amenability of peptides to customization presents a unique opportunity to overcome such difficulties.

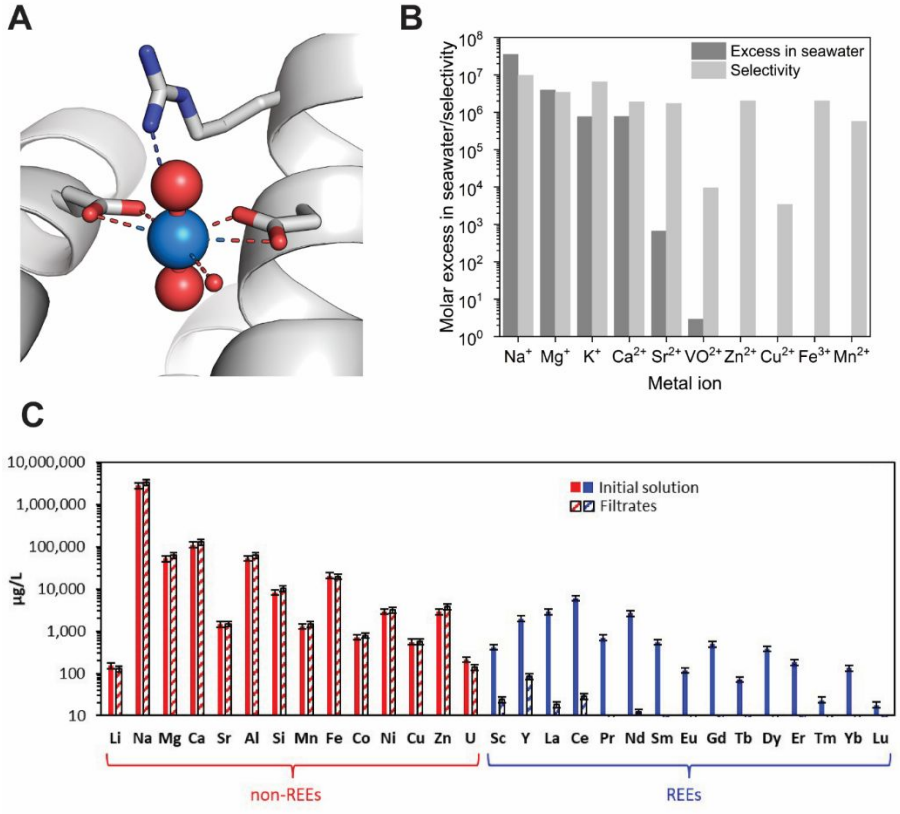
In an effort to obtain more selective ligands, the well-known binding of REEs to biological Ca^{II} sites such as EF hands[78,96,203] has been extensively exploited, using these motifs as starting point for developing REE-binding peptides.[204,205] The affinity of an isolated EF-loop for REEs is typically in the low micromolar range or slightly tighter,[206] limiting their practical application. In 2003, Imperiali and co-workers reported the in vitro screening and development of a novel EF-loop peptide with increased affinity for Tb^{III} (57 nM, pH 7.2), known as the lanthanide binding tag (LBT, **Figure 4**).[207] Other EF-hand derivatives have also been developed, including one incorporating an unnatural, polyaminocarboxylate-containing amino acid to yield femtomolar REE affinity, although metal selectivity was not determined.[208] In another example, an EF-hand derivative with enhanced, but still relatively low, affinity for uranyl was engineered (CaM-M3c: K_d = 18 μM, pH 6).[209] The costs associated with peptide synthesis have led to the exploration of cell-based methods incorporating LBTs.

The LBT/peptide and whole-cell biosorption schemes have been unified by expression of tandem (8×) LBT peptides linked to naturally occurring "anchor" proteins on the surface of *Caulobacter crescentus*.[122] The modified cells exhibited enhanced adsorption capacity (~9 mg Ln^{III} g^{-1} biomass, **Table 1**) of REEs with a modest selectivity towards HREEs. REEs were recovered through citric acid treatment, and the technology was useful over multiple adsorption/desorption cycles.[137] Although the LBT-modified cells exhibited enhanced selectivity against Ca^{II} and Mg^{II}, competitive adsorption of Cu^{II}, a common contaminant in low-grade sources, was also observed.[122,137] Furthermore, this method is complicated by the dual adsorption of REEs to the cell surface and the LBTs, with separations being complicated by differing metal selectivity and affinity for these two media. However, this challenge can be mitigated by saturation of non-specific sites with abundant ions such as Ca^{II}.[137] In another approach, 8×LBT was appended to the curli fibers, an amyloid EPS involved in biofilm formation, of *E. coli.*[138] These LBT-conjugated fibers were immobilized on filters, resulting in an adsorption capacity roughly five-times (~43 mg Ln^{III} g^{-1} curli-LBT) that of the surface-displayed LBT. Desorption was accomplished through nitric acid wash, and the curli-LBT was still highly functional after three sorption/desorption cycles.[138]

To the best of our knowledge, the first example of a protein with excellent selectivity for an f-element is the engineered protein, super uranyl-binding protein (SUP).[69] The SUP template was found by a computational screening algorithm, to search the Protein Data Bank for potential

uranyl-binding sites based on the UO_2^{2+} ion's unique *trans*-oxo structure (**Figure 5A**). Subsequent rational mutations yielded SUP, which exhibited 7 fM affinity for UO_2^{2+} (pH 8.9) and $>10^6$ selectivity for most ions except 10^4 for vanadyl (VO^{2+}) and Cu^{II} (**Figure 5B**).[69] Subsequent computational modeling allowed for a second version of SUP with slightly enhanced uranyl binding.[210] Conjugation of SUP to the spider silk protein spidroin allows for relatively rapid (days) recovery of uranyl from seawater, which contains 13 nM uranium on average, with good selectivity over other metals, although a small amount of vanadium is also recovered (**Table 1**).[142] Unfortunately, the protein loses affinity quickly at lower pHs, with a K_d of 0.2 nM at pH 6.0, which may limit its utility in other settings. Still, the excellent performance of this protein shows the possibilities for metal extraction using protein chelators.

Figure 5. Selectivity of selected engineered and natural macromolecular f-element chelators. (A) Metal binding site of the super uranyl binding protein (SUP). U^{VI} is depicted as a blue sphere with two oxo ligands shown in red. One water molecule, shown as a small red sphere, coordinates the uranyl complex in the equatorial plane.[69] (B) Molar excess of selected cations relative to uranyl found in seawater (dark gray), and the apparent selectivity of SUP for uranyl against that cation (light gray). Adapted from He and coworkers[69] with permission from Springer Nature, copyright 2014. (C) Compositions of lignite leachate (solid) and the low molecular weight filtrate (striped) after treatment with LanM (100 μM, pH 3.7), showing selective and quantitative extraction of REEs by the protein. Reproduced with permission from Deblonde et al.,[99] copyright 2020 American Chemical Society.



The discovery of the biological role of REEs indicated that natural, highly selective REE-chelators would exist. The first such chelator to be identified and characterized was the protein,

LanM.[93,94] LanM's native EF hands exhibit picomolar affinity for REEs and a gated conformational response that imparts over six orders of magnitude of selectivity for REEs over other common cations like Ca^{II}, Cu^{II}, and Mg^{II}.[93,98] In fact, to the best of our knowledge, LanM exhibits the highest affinity and selectivity for REEs of any currently known biomacromolecule, including calmodulin, transferrin, siderocalin, and lipocalin (the latter three of which require a synergistic ion chelator as well), and greater selectivity than most small molecules.[99] In addition, LanM remarkably can withstand harsh conditions (pH < 2), retains metal binding down to pH 2.5, and is stable at 95 ºC, suggesting that the protein might be sufficiently robust to recover REEs from industrially relevant feedstocks.[99] Indeed, LanM quantitatively and selectively recovers total REEs with high purity from e-waste and lignite coal leachates, in a single aqueous step (**Figure 5C**). Despite the protein's high affinity, desorption can be induced by relatively mild treatments (lowering pH or simple chelators), and can be cycled to bind and desorb REEs multiple times.[99] Although in this study the protein was not immobilized for the purposes of extraction, the data make it clear that such a strategy would enable rapid, single-step extraction of total REEs, without need for organic solvents. However, because LanM is only modestly selective for adjacent REEs, the protein would need to be engineered further for REE separation applications. The robust properties and performance of LanM suggest that this protein and its derivatives may represent a new and efficient approach for REE extraction.

5. Biological methods for f-element detection

The detection of f-elements (here we focus on REEs and uranium) is important from both environmental and industrial perspectives, such as in prospecting for new deposits or in optimization and quality control of extraction and separations processes. The average crustal abundances of REEs range from ~0.5-50 ppm, depending on REE, and for U, 2 ppm. While ~300 ppm (2 mM) is the minimum total REE standard for extraction using traditional technologies,[32] there is substantial interest in identifying and developing capacity to use lower-grade sources. As such, detection methods must be sensitive and selective. Currently, the primary detection method employed for REEs is inductively coupled plasma mass spectrometry (ICP-MS). This technique is highly sensitive (detection limits of 1 ppb in solid samples) and can give concentrations of all elements of interest in the sample, but it requires sample digestion, specialized laboratory instrumentation, and trained operators.[211] Meanwhile, portable x-ray fluorescence spectrometers are available for field use, but their applications to analysis of REEs are particularly challenging, with significant interferences, low sensitivity, and difficulty of discriminating individual REEs.[212,213] As a result, significant efforts are being directed toward less expensive and more accessible technologies for metal analysis.[32] Biological methods offer an attractive alternative, especially in applications for which inexpensive screening is desired to rapidly identify samples to subject to further, complete elemental analysis.

5.1. Probes using gene regulatory systems

One subset of biological approaches involves the adaptation of endogenous DNA-binding metalloregulatory proteins to bind selectively to the metal of interest and affect expression of a downstream reporter gene, such as encoding for a fluorescent protein. In one early approach, the Ni^{II}-dependent transcriptional repressor, NikR, was re-engineered by He and coworkers to be selective for uranyl.[214] This transcription factor was chosen for engineering because the square pyramidal geometry of the Ni^{II} binding site in the protein could serve as the equatorial ligand plane

for uranyl recognition (**Figure 5B**). Upon mutagenesis of two of these ligands and addition of a hydrogen bond donor to one of the axial oxo groups, the resulting protein selectively bound to DNA in the presence of uranyl (K_d = 53 nM for metal binding) but not Ni^{II} or other divalent transition metal ions tested. Although this approach was not tested in vivo, this work established that gene-regulatory machinery could be reengineered to interact with f-elements.

This concept was extended by He and coworkers with the development of a Ln-selective bacterial two-component system (**Figure 6A**).[215] This system was produced by replacing the Fe^{III}-binding motif of PmrB, the periplasmic component of the Fe^{III}-responsive bacterial two-component system PmrA/PmrB, with an LBT. Upon Ln^{III} binding to LBT-PmrB, the signal would be transduced to PmrA, which would activate expression of green fluorescent protein (GFP). This construct responded significantly to as little as 0.2-1 μM Tb^{III} (the Ln^{III} with highest affinity for LBT). Although little response to slightly higher concentrations of common metals was observed (e.g., 10 μM Cu^{II}, Zn^{II}, and Ca^{II}), it did respond appreciably to 50 μM Ca^{II}. Furthermore, because Ln^{III}-LBT affinity decreases on either side of Tb^{III},[121] this method may not be as effective for other REEs. These issues reflect the challenges of using LBTs in extraction applications (section 4.4).

Taking advantage of the ability of *M. extorquens* to uptake and sense LREEs La-Nd (although the full mechanism by which this regulation occurs is not yet understood), the groups of Martinez-Gomez and Skovran fused the gene encoding the fluorescent protein Venus to the *xoxF1* promoter, enabling detection of ~2.5 nM La^{III} within several hours.[108] This system is also able to detect Nd from a crushed hard drive magnet.[51] This reporter is a promising biological approach for sensitive detection of the elements La-Nd as a group, the most abundant of the REEs in the environment.

5.2. Protein-based sensors

Molecular methods of metal detection likely enable greater speed and potentially a wider range of sample conditions than cell-based approaches. The identification of selective Ln-binding proteins[93,98] has enabled the development of a protein-based fluorescent sensor for REEs. Protein-based Förster resonance energy transfer (FRET) sensors have been developed for many analytes[216] and for other metal ions such as calcium and zinc.[217] In this approach, a protein that undergoes a conformational change in response to an analyte of interest is linked to a FRET donor (commonly enhanced cyan fluorescent protein, ECFP) and acceptor (commonly yellow fluorescent protein, YFP); upon analyte binding, the protein's conformational change alters the distance and relative orientations of these fluorophores, altering the ratio of the ECFP and YFP emission intensities. We exploited the large, REE-selective conformational change exhibited by LanM in order to generate a sensitive (10 nM limit of detection, ~1 ppb) FRET-based sensor, called LaMP1, for REEs that retained the protein's picomolar affinity and high selectivity for REEs, with only negligible responses to competing metal ions at concentrations relevant to low-grade REE feedstocks (**Figure 6B**).[98]

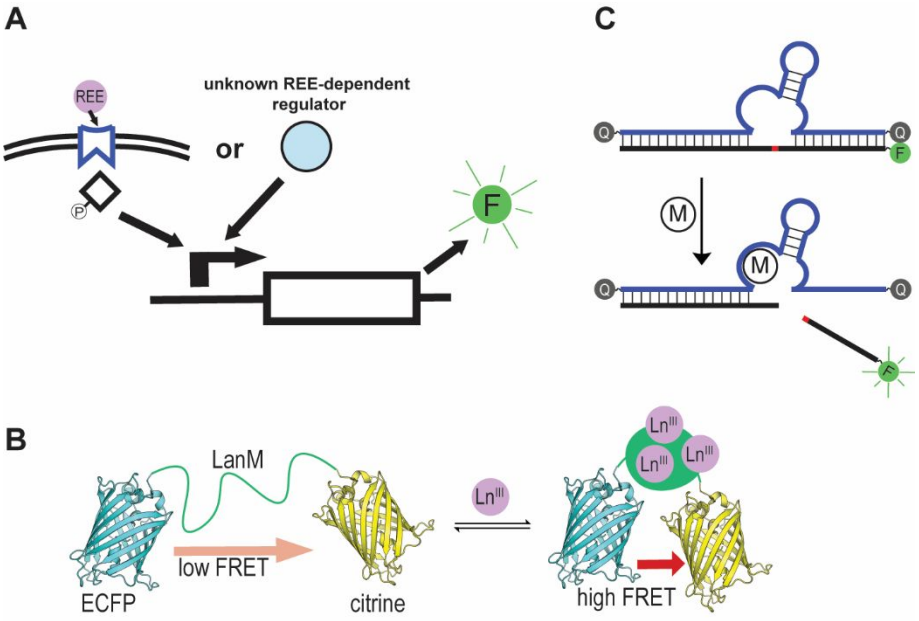
We initially applied LaMP1 in vivo to uncover details about LREE uptake in methylotrophs, but the sensor also demonstrates more generally that LanM can be used as the basis for methods of rapid sensing total REEs in a sample. However, several improvements would be necessary before applicability in the field, including a derivative more suitable for turbid, low-pH samples and improved selectivity within the REE series. Finally, it has not yet been established whether LanM, and consequently LaMP1, would be able to directly enable REE detection and/or extraction from solids, which would also facilitate use in the field.

5.3. DNA-based sensors

An alternative approach to metal detection uses synthetic, catalytic DNAzymes.[218,219] For the purpose of metal ion detection, these molecules consist of two annealing strands, "substrate" (appended to a fluorophore) and "enzyme" (appended to a fluorescence quencher). Upon metal binding, the substrate strand backbone is cleaved at a specific position (often a single ribonucleotide inserted into the substrate), the strands dissociate, and a fluorescence signal is produced (**Figure 6C**). In vitro selection methods have been used to create both uranyl-[218,220–222] and REE[223]-selective DNAzymes. In the case of fluorescence-based sensors for uranyl, the limit of detection is 45 pM, with a dynamic range extending to 400 nM. Optimum sensor performance was at pH 5.5, but researchers suggested that alterations to the selection process may produce sensors optimized for different pHs.[220,221] DNAzymes can also be conjugated to other moieties for other sensing modalities;[218] for example, when linked to gold nanoparticles, DNAzyme cleavage changes the nanoparticles' aggregation state, creating an observable color change.[222] In the case of REEs, the problem of selectivity within the lanthanide series has been addressed by evolving five DNAzymes, each with different selectivity patterns, and deconvolving the responses using a computational algorithm to identify specific REEs.[223] However, such an approach would likely not be able to quantify the individual REEs in a complex mixture of multiple REEs.

The adaptability and relative ease of screening to select for new aptamers[218,224] make DNA-based sensors attractive possibilities for future development. Furthermore, in these systems, selectivity of detection can originate not just from metal binding selectivity but also from the catalytic step. Unfortunately, however, the paucity of structural information for metal-bound DNAzymes limits knowledge of the principles that govern their metal selectivity.

Figure 6. General designs for biological REE sensing approaches. (A) In a cell-based reporter, activation of a two-component system response regulator in an REE-selective manner induces expression of a fluorescent protein-encoding gene.[108,215] (B) Schematic for the FRET-based REE sensor, LaMP1. REE-binding to the EF-hands of LanM induces a conformational change, driving a FRET response. Adapted from Mattocks et al.[98] (C) In a DNAzyme-based probe, binding of substrate (M) induces the cleavage of the fluorophore-containing segment of substrate DNA (F). This action separates the fluorophore from the quencher (Q), enhancing fluorescence. Adapted from ref. 220 with permission from the National Academy of Sciences U.S.A., copyright 2007.



6. Conclusions and future outlook

Exploiting biology and/or biomolecules to harvest and sense and separate REEs and other desirable metals is not a new idea. However, it is only recently that investigations have begun to uncover biology's selective tools for achieving these goals. While it is too early to analyze the economics of implementation of technologies based on these findings, they have potential to be competitive, especially if they are recyclable, can minimize the need for very low pHs for metal solubilization and organic solvents for extraction, and if high affinity and selectivity of biological systems allows applicability to currently abundant but inaccessible low-grade sources. Utilization of biological ligands for these methods has two other notable, unique advantages. First, biological frameworks like proteins and small molecules involved in metal uptake enable not only more subtle, and highly evolved, tuning of coordination chemistry at the metal site but also contributions from non-covalent interactions distal to the metal-binding site (e.g. hydrophobic packing) in order to achieve high affinity and high selectivity. Second, biology is easily used as a tool for modulation of function via both rational engineering and directed evolution approaches. We envision that some of the exciting opportunities in this area include:

1) Using methylotrophs for concentration of REEs. The simplest approach conceptually is to add a methylotroph such as *M. extorquens* to concentrate LREEs in lanthanosomes, which could then be isolated. Even within the LREEs, La uptake seems to be preferred over Nd in *M. extorquens*,[110] so large separation factors may be obtainable from such a process. REE-utilizing organisms may be limited to accumulating LREEs (e.g. separating Nd from Dy in e-waste), and it is unclear the extent to which HREEs or other abundant trivalent metal ions (which might bind to secreted chelators but not allow uptake) would interfere with these pathways. Applications of organisms to raw and low-grade REE feedstocks like coal leachates may be particularly challenging due to high concentrations of contaminants (e.g. heavy metals) that may be toxic to the bacteria, necessitating addition of heavy metal detoxification systems.[51] Continued work to identify new REE-utilizing organisms is critical to uncover diverse lanthanophores and potentially organisms with different REE preferences. It may also be possible to evolve the Ln^{III} preferences of certain methylotrophs

towards the HREEs via in vitro selections. However, the percentage differences in ionic radius for adjacent HREEs are significantly smaller than for the LREEs, making HREE separations an especially challenging problem.

2) Bio-derived and bio-inspired lixiviants. Major advantages of molecular harvesting and separation systems include: 1) accessibility to chemical synthesis (although natural molecules could also be collected from culture supernatants, if convenient), 2) the ability to make derivatives of natural chelators with altered or improved properties, e.g. HREE responsiveness, 3) avoiding potential toxicity to biological systems and thus applicability to a wider variety of metal feedstocks, and 4) potential interfacing with existing industrial solvent extraction schemes for collection of REE-lixiviant complexes. Characterization of a broader array of biological ligands can also enable application of the core structural motifs and guiding principles to other strategies, such as peptoid-based chelators, or integration into novel chromatography,[37] MOF,[225] PAF,[43] or other systems to increase their selectivity.

3) Synthetic REE-harvesting organisms. It may be sufficient to insert complete lanthanide uptake and utilization pathways into a faster growing, heterologous system with no native REE-dependent pathways, such as *E. coli*, or in an organism that is naturally more metal-resistant (e.g. *Cupriavidus metallidurans*), or to remove regulation to maximize uptake. This approach could be particularly useful if selectivity of methylotroph REE uptake is governed by multiple factors, not merely REE-lanthanophore affinities.

4) Protein-based extraction and separation. Proteins are commonly considered too fragile for industrial applications because most are unstable at pH extremes and high temperature, and they are relatively large molecules. However, LanM (for REEs) and SUP (for uranium) are small, robust proteins with performance that rivals or exceeds that of many small-molecule chelators, suggesting that these unconventional industrial ligands merit more consideration. Of course, continuing work may uncover even more proteins with useful properties. For proteins to be viable technologies, however, robust yet inexpensive immobilization methods will be key. A particular advantage of proteins is their facile in vitro evolution, enabling screening to generate new, selective chelators for other metals of interest, via both rational and random screening approaches.

5) Biomolecular sensors for f-elements. Cell-, protein-, and DNA-based biosensors for REEs have been developed, with similar, nanomolar (~ppb) limits of detection, which is sufficient for translation into portable technologies for REE detection in the field. Although quantification of total REEs is useful in a sample, a major challenge of these approaches is the discrimination of individual REEs, which would be substantially more powerful. It may be possible to integrate methods that exploit the unique luminescence properties of many Ln^{III} ions,[226] into these platforms to enable quantification of individual REEs so that methods like ICP-MS might be avoided entirely.

6) Applications in medicine. The same ideas that motivate exploration of bio-derived chelators in biomining and sensing also suggest their potential value in medical applications. Complexes of the trivalent REEs and f-block elements have many well-established and emerging applications as imaging and therapeutic agents, for example Gd-based MRI contrast agents,[17] ^{177}Lu and ^{225}Ac radiopharmaceuticals,[227] and Sc and Y isotopes for positron emission tomography (PET)

imaging.[228,229] However, man-made chelators often present significant challenges, including slow labeling kinetics at room temperature, rapid clearance within the biological system, and partial retention of Gd^{III} in patients after use of contrast agents.[18] The high selectivity and high stability constants yet rapid binding kinetics exhibited by LanM[98,99] and likely other biological REE complexes could facilitate these applications, and more.

In closing, the rapidly increasing understanding of the biomolecules that biology uses to recognize REEs offers the potential to revolutionize the industrial methods used to extract, separate, and detect REEs and actinides – both through direct utilization of naturally occurring or engineered biomolecules and through using these ligands as inspiration for other strategies. Preliminary studies have shown that these ideas are feasible, although much work remains to be done. In reality, there is unlikely to be a single optimal solution for all applications. Translating these biological and biochemical observations into viable technologies will require collaboration between biologists, biochemists, synthetic chemists, and engineers. These efforts will be critical in order to achieve an environmentally sound and sustainable supply of f-block elements for ever-expanding applications in the 21st century.

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Notes
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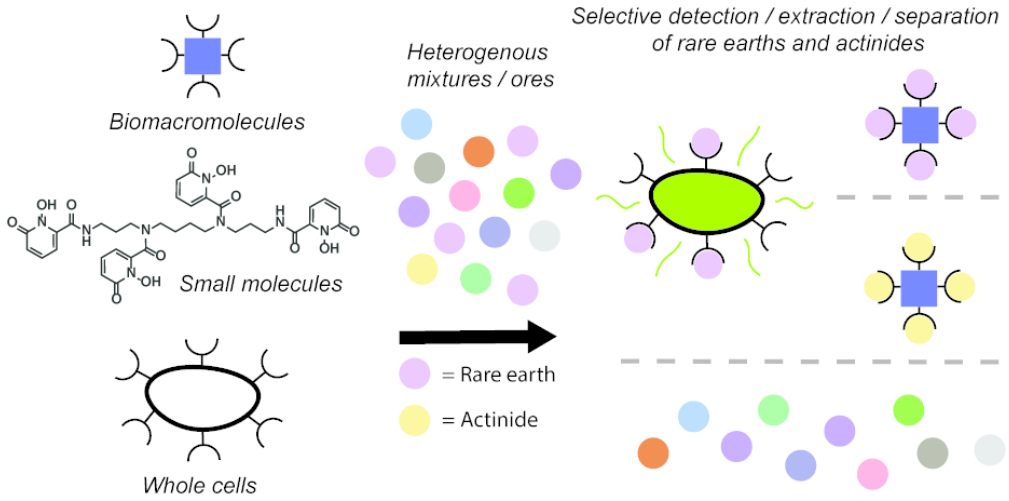
Biomacromolecules
Small molecules
Whole cells
Heterogenous mixtures / ores
= Rare earth
= Actinide
Selective detection / extraction / separation of rare earths and actinides