



Campaign Community Science Meeting Report

# Metal Binding Biomolecules

November 2025

William Kew



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# **Metal Binding Biomolecules**

November 2025

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## Introduction

This report summarizes the outcomes of a Community Science Meeting focused on fundamental scientific questions surrounding metal-binding biomolecules and metal selectivity in biological systems, held in November 2025 at the Environmental Molecular Sciences Laboratory (EMSL). The meeting was convened to inform the potential development of a Community Science Campaign titled “Discovery and Characterization of Critical Metal-Binding Small Molecules and Proteins (Metal-Binding Biomolecules).”

The Community Science Meeting was organized as part of a broader campaign planning effort that also included discussions of two additional Critical Minerals and Materials (CMM) research campaigns. Together, these meetings were designed to gather community input on distinct but complementary scientific frontiers relevant to the Department of Energy (DOE) Biological and Environmental Research (BER) program mission.

The meeting was explicitly designed as a scientific framing and community input exercise, rather than as a mechanism for funding decisions or campaign governance. Participants were asked to identify core scientific challenges, measurement bottlenecks, and integration opportunities that currently limit progress in understanding how biological systems interact with, discriminate among, and utilize metals. The discussion emphasized discovery-scale science and sought to clarify where a coordinated, campaign-style approach—leveraging EMSL’s integrative capabilities—could enable advances that are difficult to achieve within individual laboratories.

Across discussions, participants converged on metal selectivity across scales as the unifying scientific theme. Selectivity was framed as an emergent property arising from coordinated chemical and biological processes, rather than from isolated binding events. Participants emphasized that metal binding alone is insufficient to establish biological relevance, and that functional significance must be interpreted in biological context. Current research efforts were viewed as limited by fragmentation across scales and methodologies, motivating the need for more integrated approaches, particularly for metals of interest to DOE priorities, including critical and near-critical elements.

In this context, EMSL was discussed as a discovery-scale, integrative user facility capable of supporting coordinated, multi-modal investigations of metal selectivity across scales. Rather than acting as a provider of isolated measurements, EMSL’s value was framed around the intentional integration of complementary analytical approaches—spanning molecular characterization, quantitative metal analysis, structural insight, and spatially resolved measurements—to address questions linking molecular identity, localization, and biological function.

This report synthesizes the scientific themes, opportunities, and design considerations that emerged from the Community Science Meeting discussions. It reflects areas of strong community alignment as well as key uncertainties and boundary conditions that will shape future campaign development. The document serves as the public record of the meeting and is intended to inform the potential development of a Community Science Campaign focused on metal selectivity across biological scales.



## Acronyms and Abbreviations

BER	Biological and Environmental Research
CMM	Critical minerals and materials
DOE	Department of Energy
EMSL	Environmental Molecular Sciences Laboratory



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## 1.0 Community Science Meeting Scope and Framing

The Community Science Meeting was convened to help define how a coordinated, discovery-scale research campaign focused on metal-binding biomolecules could most effectively advance scientific understanding aligned with DOE BER priorities. The intent was to engage the research community in shaping the scientific focus of such a campaign, identifying key challenges, and articulating where a campaign-style approach could provide the greatest value. The discussion was framed to inform campaign goals, scope, and enabling strategies without prescribing specific projects or experimental designs.

Discussions were structured to move from broad scientific frontiers toward more concrete considerations of measurement needs and campaign organization. Participants were encouraged to identify scientific questions that are difficult to address within individual laboratories, particularly those requiring integration across multiple analytical scales or coordination of complementary capabilities. The meeting emphasized synthesis and cross-cutting challenges that could benefit from a shared, user-enabled research framework.

The participant cohort included external scientists from academia and national laboratories, representing a range of disciplines including microbiology, biochemistry, analytical chemistry, mass spectrometry, spectroscopy, imaging, structural biology, and computational analysis, and spanning diverse career stages. These external participants were the primary contributors of scientific perspectives and community priorities. EMSL staff participated to help guide discussion, clarify facility-relevant considerations, and prompt dialogue without prescribing outcomes. Participation reflected a range of biological systems, from genetically tractable model organisms to environmentally and industrially relevant contexts, enabling discussion of both mechanistic depth and real-world complexity.

The Community Science Meeting was framed around discovery-scale, fundamental science, with discussion intentionally bounded away from process optimization, scale-up, or applied separations. Participants were asked to consider metal-binding biomolecules across diverse biological systems and metals, without restricting scope to a single element, organism, or molecular class. To support meaningful comparison while preserving biological relevance, the discussion acknowledged the need to balance shared reference points with flexibility in experimental systems with the understanding that specific design choices would be addressed in later stages of campaign development.

Overall, the Community Science Meeting established a shared understanding of scope, priorities, and boundaries for a potential campaign on metal-binding biomolecules. The discussions provided a foundation for articulating a coherent scientific theme—metal selectivity across scales—while preserving flexibility in experimental approaches and biological systems. These framing elements informed subsequent discussion of scientific opportunity areas, measurement needs, and campaign design considerations.



## 2.0 Core Scientific Theme: Metal Selectivity Across Scales

Across the meeting, participants converged on metal selectivity across scales as the central scientific challenge motivating a potential campaign on metal-binding biomolecules. This framing emerged organically and was repeatedly invoked as participants described knowledge gaps, experimental limitations, and opportunities for discovery. Importantly, metal selectivity was not treated as a single molecular property, but as an emergent phenomenon arising from coupled chemical and biological processes operating across multiple spatial and organizational scales.

At the molecular scale, selectivity is influenced by coordination chemistry, ligand identity, geometry, oxidation state, and kinetic versus thermodynamic effects. At this scale, many small molecules and coordination environments exhibit inherently broad or “promiscuous” metal-binding behavior, particularly under simplified or *in vitro* conditions. Participants noted that small changes in ligand environment or solution conditions can dramatically alter relative affinities among chemically similar metals, especially for transition metals and lanthanides. While such molecular-level effects are well recognized, participants emphasized that they rarely translate directly into biological specificity without additional layers of control.

At the protein and pathway scale, selectivity is shaped by regulated transport systems, metalloproteins, and intracellular handoff mechanisms. As a consequence of chemically permissive binding at the molecular level, many proteins and metabolites display broad binding behavior under simplified or *in vitro* conditions. Participants emphasized that affinity measurements alone are therefore insufficient to explain observed biological behavior, and that selectivity at this scale reflects regulation, competition, and context-dependent interactions rather than intrinsic binding strength in isolation.

At the cellular and systems level, selectivity was frequently discussed in terms of a “metal economy” by analogy to nutrient economies. In this framing, metals are sensed, acquired, allocated, trafficked, stored, and excluded according to cellular priorities and environmental constraints. Selectivity emerges from the coordinated management of scarcity, toxicity, and functional demand, rather than from any single binding event. Participants emphasized that mis-metallation, competitive inhibition, and dynamic redistribution are central features of this metal economy and remain poorly constrained experimentally.

Beyond individual cells, participants highlighted the importance of community and environmental context. In complex systems, gradients, competition, cooperation, and shared metabolites can shape collective metal-handling strategies that cannot be inferred from single-organism studies. Several participants noted that community-level behaviors may invert or obscure selectivity trends observed in model systems, underscoring the need to explicitly consider scale when interpreting measurements.

A key point of convergence throughout the meeting was the explicit distinction between metal binding and biological function. Participants emphasized that demonstrating binding—particularly under controlled or artificial conditions—does not establish biological relevance. Functional significance must be supported by evidence from phenotyping, transport measurements, imaging, or system-level responses. This distinction was treated as foundational, with implications for experimental design, data interpretation, and claims of selectivity.

Participants also identified a persistent challenge in bridging scales. Current studies often produce high-quality but isolated datasets: binding constants without cellular context, omics signatures without mechanistic grounding, or structures without functional validation. These disconnected “snapshots” limit the ability to develop predictive or generalizable understanding of metal selectivity. Addressing this gap was viewed as a defining scientific opportunity for a coordinated campaign.



Taken together, these discussions established metal selectivity across scales as both the unifying scientific theme and the primary source of difficulty in this field. Participants emphasized that progress will require intentional coupling of complementary measurements, careful attention to context, and experimental designs that explicitly link molecular detail to biological outcome. This framing informed subsequent discussions of specific scientific opportunities, measurement needs, and campaign design considerations.



## 3.0 Key Scientific Opportunity Areas

Building on the unifying theme of metal selectivity across scales, participants identified a set of scientific opportunity areas where coordinated, discovery-scale efforts could substantially advance understanding. These areas reflect both shared scientific priorities and common experimental bottlenecks discussed throughout the Community Science Meeting. While conceptually distinct, they are deeply interconnected and were frequently discussed together, particularly where biological processes and measurement context intersect.

### 3.1 Metal Binding, Affinity, and Selectivity in Context

A dominant opportunity identified by participants was the need to move beyond isolated affinity measurements toward a more contextualized understanding of metal binding. While binding constants and *in vitro* assays remain essential, participants emphasized that such measurements frequently fail to predict biological behavior in complex environments.

Key challenges discussed included distinguishing biologically meaningful selectivity from promiscuous binding, accounting for competition among metals present at physiologically relevant concentrations, and reconciling discrepancies between *in vitro* and *in vivo* observations. Participants noted that selectivity often depends on subtle differences in coordination environment, kinetics, and regulation that are difficult to capture using single-technique approaches.

A coordinated campaign was viewed as an opportunity to generate comparative datasets under well-defined chemical and biological conditions that probe how binding behavior varies across conditions, ligands, and biological states, enabling identification of generalizable principles rather than system-specific descriptions.

### 3.2 Transport, Trafficking, and Spatial Determinants of Metal Function

Participants emphasized that understanding metal selectivity requires insight into what happens after metal uptake, including transport, intracellular trafficking, compartmentalization, and redistribution. These processes were viewed as central to biological selectivity—particularly for avoiding mis-metallation and managing toxicity—yet remain poorly constrained experimentally. Participants noted that post-uptake fate cannot be separated from spatial context, as where metals and metal-binding biomolecules reside within cells, tissues, or communities strongly influences function, regulation, and competition.

As a result, this opportunity area was framed around the intentional coupling of molecular characterization with spatially resolved and functional measurements. Imaging approaches were discussed not as standalone tools, but as essential components for interpreting transport and trafficking processes and for linking binding events to biological outcomes. Participants stressed that the value of such measurements lies in mechanistic insight rather than throughput, and that even small numbers of well-chosen spatial measurements can substantially constrain hypotheses about selectivity and function.

### 3.3 Low Abundance and Low-Input Metal-Binding Systems

A pervasive constraint across systems discussed at the meeting was limited material availability. Many metal-binding small molecules, proteins, and transport-associated components are present at microgram to sub-milligram levels, rendering conventional structural, kinetic, and thermodynamic approaches impractical.



Participants emphasized that the ability to operate under low material input is not a niche requirement, but a defining feature of biologically realistic systems. As a result, there was strong interest in experimental approaches that can extract meaningful information under severe material constraints, including relative or proxy measurements and tiered strategies that prioritize depth over throughput.

A coordinated campaign was viewed as an opportunity to establish and validate reusable low-input measurement approaches, reducing redundant method development and improving comparability across diverse biological contexts.

### **3.4 Data Quality, Comparability, and Modeling Readiness**

Participants identified data-related challenges as a cross-cutting scientific opportunity. Existing datasets often suffer from inconsistent annotations, uncertain metal identities or oxidation states, and incomplete metadata, limiting their reuse and integration across studies and modeling efforts.

There was broad agreement on the need for high-confidence, well-documented benchmark datasets suitable for reuse, comparative analysis, and model validation. Participants emphasized that such datasets would enable iterative experiment–model feedback and help constrain computational approaches that currently struggle to represent metal coordination chemistry accurately, particularly for chemically complex metals.

This opportunity was framed around improving data quality and comparability while preserving flexibility across biological systems, enabling shared insights to emerge without suppressing biological diversity.



## 4.0 Measurement and Capability Needs

Discussions emphasized that advancing understanding of metal selectivity across biological scales requires coordinated measurement strategies that intentionally link molecular identity, metal content, spatial localization, and biological response. Rather than focusing on individual techniques, participants framed measurement needs in terms of the types of information required to resolve scientific uncertainty and to support integrated interpretation across scales.

### 4.1 Molecular and Chemical Characterization of Metal-Binding Biomolecules

Participants emphasized the importance of accurately identifying metal-binding small molecules and proteins, resolving their composition, metal occupancy, and binding partners. High-resolution mass spectrometry was highlighted as a foundational capability for this effort, particularly for distinguishing closely related molecular species, metal adducts, and heterogeneous populations.

Capabilities such as ultrahigh-resolution Fourier transform ion cyclotron resonance mass spectrometry, liquid chromatography coupled with tandem mass spectrometry, and native mass spectrometry enable detailed characterization of metal-associated biomolecules under conditions that preserve noncovalent interactions. These approaches are particularly valuable for interrogating binding stoichiometry, metal competition, and condition-dependent binding behavior that cannot be inferred from bulk assays alone.

Quantitative metal analysis was identified as an essential complement to molecular characterization. Techniques such as inductively coupled plasma mass spectrometry and liquid chromatography-inductively coupled plasma mass spectrometry provide critical information on metal content, relative abundances, and metal-to-ligand ratios, especially when integrated directly with molecular identification workflows. Participants noted that comparative and trend-based measurements are often more informative than absolute quantification, particularly under low-input constraints.

### 4.2 Structural and Conformational Insight Under Biologically Relevant Conditions

Structural information was discussed as an important but challenging component of understanding metal selectivity. Participants noted that many metal-binding biomolecules are flexible, heterogeneous, or condition-dependent, limiting the applicability of traditional high-resolution structural approaches.

Rather than treating full structure determination as a prerequisite, participants emphasized tiered and complementary structural strategies. Capabilities such as cryo-electron microscopy, micro-electron diffraction, and solution nuclear magnetic resonance provide varying levels of structural and conformational insight depending on sample availability and system behavior. Partial structural constraints, conformational ensembles, and metal-dependent structural changes were viewed as highly informative when interpreted alongside chemical and functional data.

Participants also noted that structural measurements are often weakly constrained with respect to metal identity, coordination geometry, and occupancy, highlighting an opportunity for improved methodological development and cross-technique integration to enhance interpretability.



### 4.3 Spatially Resolved and Functional Measurements

Spatially resolved measurements were emphasized as central to interpreting metal selectivity in biological context, particularly for determining where metals and metal-binding biomolecules reside and how localization relates to function. Participants discussed imaging approaches as essential for resolving redistribution in response to environmental or genetic perturbations.

Capabilities such as nanoscale secondary ion mass spectrometry were highlighted for their ability to visualize metal distributions at subcellular scales, especially when combined with isotopic labeling or correlative measurements. Participants emphasized that spatial measurements are most informative when paired with molecular and chemical characterization, allowing localization data to directly inform mechanistic interpretation.

Functional measurements, including phenotypic assays, perturbation studies, and comparative growth or stress responses, were identified as critical anchors for interpreting binding and localization data and for establishing biological relevance.

### 4.4 Low-Input and Multimodal Workflow Integration

Across all measurement domains, participants emphasized that low-input capability is a defining requirement rather than an optimization. Many biologically relevant metal-binding systems cannot be produced or isolated in large quantities, necessitating workflows that extract maximal information from limited material.

Participants highlighted the value of experimental designs that enable multiple measurements on shared samples or closely related sample sets, preserving contextual consistency and reducing redundant preparation. Multimodal workflows linking mass spectrometry, metal quantification, structural probes, and imaging were viewed as essential for building coherent interpretations across scales.

### 4.5 Integrated Discovery: Existing and Emerging Capability Needs at EMSL

Participants identified several areas where existing EMSL capabilities, combined with targeted methodological development, could further strengthen a campaign on metal-binding biomolecules. These included improved approaches for handling extremely low-abundance samples, strategies for preserving native metal–biomolecule interactions during analysis, and tighter integration of metal-specific information into structural and imaging workflows. These needs were discussed as extensions of current strengths rather than as prescriptive requirements.

Participants also highlighted the importance of improved data integration, visualization, and analysis approaches capable of linking heterogeneous datasets across scales. While specific tools or solutions were not prescribed, there was broad agreement that the ability to connect molecular, chemical, structural, spatial, and functional data would be essential for extracting mechanistic insight and supporting iterative experiment–model feedback.

In this context, EMSL was consistently framed as an enabling platform for integrated discovery, defined not by individual instruments alone, but by its ability to support intentional multimodal workflow design, shared sample handling, and coordinated data generation within a user facility environment. Participants emphasized that the success of a potential campaign would depend not only on access to advanced measurement capabilities, but on thoughtful coordination, data quality, and the ability to iteratively refine experimental strategies as insight emerges.



## 5.0 Campaign Design Considerations and Boundaries

In addition to identifying scientific opportunities and measurement needs, the meeting also addressed how a coordinated campaign on metal-binding biomolecules could be structured to maintain scientific focus and feasibility. These discussions surfaced key design considerations, boundaries, and open questions intended to inform subsequent campaign planning, rather than to finalize implementation.

A central consideration was the balance between integration and flexibility. Participants agreed that the scientific challenges associated with metal selectivity across scales require coordinated, multimodal measurements and shared experimental context, while cautioning against overly prescriptive designs that could limit participation or exclude biologically informative systems. This tension between coherence and openness was treated as a design feature rather than a flaw.

Participants discussed the role of benchmark systems and reference materials in enabling comparability across projects. Such benchmarks were viewed as valuable for methodological development and cross-project synthesis, provided they complement rather than replace investigator-driven biological systems. Maintaining this balance was identified as an important consideration for campaign governance.

Scope definition was also a recurring topic. Participants emphasized that the campaign should not be organized around a single metal, organism, or molecular class. Although lanthanides and rare Earth elements were frequently discussed due to recent discoveries, value was seen in identifying principles of metal selectivity that extend across multiple metals and biological contexts.

The temporal and experimental scale of campaign activities was similarly considered. Participants favored depth over breadth, noting that a smaller number of well-integrated studies would be more informative than a large collection of loosely connected datasets. This perspective reinforced the emphasis on discovery-scale science rather than high-throughput screening or exhaustive surveys.

Participants also acknowledged uncertainties related to data integration and interpretation. Even with coordinated measurements, linking molecular identity, metal content, spatial localization, and biological function remains challenging. The campaign was therefore expected to support iterative refinement of hypotheses and workflows as insights emerge, rather than enforcing fixed analytical pipelines from the outset.

Finally, clear boundary conditions were articulated regarding what the campaign is not intended to address. The effort was not framed as an applied engineering program, a process optimization initiative, or a platform for scale-up of metal recovery technologies. While relevance to critical minerals and materials provides important motivation, success was defined in terms of advancing fundamental, mechanistic understanding.

Taken together, these considerations underscore that a successful campaign will require thoughtful design that balances coordination with flexibility, depth with accessibility, and ambition with feasibility. The Community Science Meeting established a shared framework to guide subsequent campaign development.



## 6.0 Implications and Path Forward

The Community Science Meeting established a clear scientific rationale for a coordinated research campaign focused on the discovery and characterization of critical metal-binding small molecules and proteins, framed around the unifying challenge of metal selectivity across biological scales. Across diverse disciplines and biological systems, participants demonstrated strong alignment on both the importance of this problem and the limitations of existing, fragmented approaches.

Discussions highlighted that metal selectivity cannot be understood through isolated measurements or single-scale analyses. Progress will require intentional integration of molecular characterization, quantitative metal analysis, structural insight, spatial localization, and functional context—an effort that exceeds the scope of most individual laboratories and is well suited to a coordinated, campaign-style approach.

This report captures areas of consensus as well as key uncertainties and design considerations that emerged during the meeting. Rather than prescribing specific systems or workflows, it outlines a scientific framework and set of opportunity areas to guide future campaign development while preserving flexibility and inclusivity.

Within this context, EMSL was identified as a uniquely enabling user facility for advancing this science, based on its ability to support integrated measurement strategies and coordinated data generation across complementary capabilities. Participants emphasized that the value of a potential campaign lies in enabling and accelerating user-driven, BER-relevant research, rather than defining or executing a fixed set of internal scientific projects. The emphasis on discovery-scale science, low-input systems, and multimodal integration reflects the community's view of where the greatest scientific leverage lies.

Taken together, the scientific themes and considerations outlined here provide a foundation for continued engagement with the user research community and for the potential development of a coordinated campaign focused on metal-binding biomolecules and metal selectivity across scales.



## 7.0 Participants

### External

Allegra Aron – University of Denver

Rene Boiteau – University of Minnesota

Norma Cecilia Martinez Gomez - University of California, Berkeley

Patrick Chain – Los Alamos National Laboratory

Yongqin Jiao – Lawrence Livermore National Laboratory

Qun Liu – Brookhaven National Laboratory

Arvind Ramanathan – Argonne National Laboratory

Aaron Robinson – Los Alamos National Laboratory

Brian Sanders – Oak Ridge National Laboratory

Emily Smith – Ames National Laboratory

Ning Sun – Lawrence Berkeley National Laboratory

Anna Vietmeier – National Energy Technology Laboratory /Duquesne University

Allison Werner – National Laboratory of the Rockies

Peng Xu – Ames National Laboratory

### Internal

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Kristin Burnum-Johnson – Functional and Systems Biology Science Area Leader

Scott Baker – Microbial Molecular Phenotyping Science Area Leader

James Evans – Structural Biology Integrated Research Platform Leader

Alex Beliaev – Integrated Research Platform Leader

Paul Piehowski – Biomolecular Pathways Integrated Research Platform Leader

Christopher Anderton – Microbial Biotechnology Campaign Leader

Samantha Miller – Project Manager

Liz Eder – Project Manager

