Metals such as copper and iron are essential micronutrients in biology, as their redox activities facilitate basic cellular processes ranging from antioxidant defense to respiration along with emerging regulatory roles in cell signaling. However, this redox activity can be detrimental when their homeostasis is disrupted, leading to oxidative stress and damage associated with diseases. The context in which a metal resides within a biological environment significantly influences its activity in function. Recent years have seen a rise in tools for monitoring metal ions and have illuminated the diversity in metal speciation in biology, but many of these tools are focused on probing metals in the intracellular space. The state-of-the-art methods for assessing metal status in extracellular fluids such as blood plasma focus either on absolute quantitation or evaluate a limited number of metal-containing species. While these methods have offered important insight into extreme cases of metal deficiency in overload, subtle imbalances are more challenging to diagnose and understand with the available methods. This talk will describe our efforts to expand and elucidate the metal speciation of the extracellular space, specifically in the blood plasma. Specifically, I will discuss our approaches to understanding the interactions of metals with peptide hormones in the context of the protein-rich blood plasma and the complementary development of chemical biology tools for investigating metals and metal-containing species in this milieu. We focus our studies on connecting extracellular metal dynamics to the diagnosis and prognosis of metabolic diseases like diabetes and fatty liver disease.