The number of proteins in the UniProt database (>182M sequences in Release 2019_10) is increasing with a doubling time of ~2.5 years; however, ≥50% of the proteins have uncertain, unknown, or incorrect functions. This lecture will describe the Enzyme Function Initiative web resource for genomic enzymology tools for leveraging the protein, genome, and metagenome databases to discovery novel enzymes and metabolic pathways. The resource includes tools for 1) generating protein sequence similarity networks (SSNs; EFI-EST; efi.igb.illinois.edu/efi-est/) to explore sequence-function space in protein families, 2) generating genome neighborhood networks (GNNs; EFI-GNT; efi.igb.illinois.edu/efi-gnt/) for identifying functionally linked genes/proteins in metabolic pathways, and 3) chemically guided functional profiling (CGFP) for mapping metagenome abundance to clusters in SSNs (EFI-CGFP; efi.igb.illinois.edu/efi-cgfp/). Examples will be given of metabolic pathways that have been discovered using these tools. The lecture also will describe development of a new web resource (“radicalSAM.org”) to facilitate access to the very large radical SAM enzyme superfamily (512K sequences). Supported by NIH U54GM093342 and P01GM118303.