EXPLORING SEQUENCE-FUNCTION SPACE IN THE OLD YELLOW ENZYME SUPERFAMILY

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Biotechnology and bioinformatics have made it increasingly apparent that there is a vast wealth of protein 'dark matter', i.e., sequence and functional information that is yet to be discovered and harnessed for fundamental or applied gains. For example, the superfamily of Old Yellow Enzymes (OYEs) with ~88 characterized enzymes in the literature, is shockingly underexplored, despite >85 years of research and their proven industrial application. We have applied large scale bioinformatic and synthetic biology approaches to systematically sample and functionally characterize >120 representatives across the entire OYE superfamily, which is comprised of >70,000 members. Our efforts have more than doubled the current OYE knowledgebase and have yielded native biocatalysts with improved activity and expanded substrate specificity. Furthermore, our multidisciplinary approach serves as an adaptable pipeline for the analysis of other superfamilies, improving the current standard of investigative processes for the field. The comprehensive characterization of enzyme superfamilies, especially those with proven biocatalysis capabilities, offers tremendous opportunities for future developments of green and sustainable chemical processes.