426g High-Throughput Biocatalysis on Microarrays for Synthesis and Screening of Small Molecule Therapeutics

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There is a tremendous need to develop new tools for generating small molecule based therapeutics and screening them in a rapid and high-throughput manner. Solid-phase biocatalysis is a powerful tool that can be used to generate bioactive small molecules by exploiting the unique selectivity of enzymes combined with the advantages of solid-phase reactions such as simple purification and isolation of a single compound from a mixture. Using principles of solid-phase biocatalysis and microarray technology, we have generated a library of phenolics with potential therapeutic significance, in a spatially addressable format in 25 nL reaction volumes on glass slides. Apocynin, an ortho-methoxyphenol known for its antioxidative properties was used as a model compound along with peroxidase-catalyzed phenolic oxidation to generate molecules that were screened for their thiol-binding ability. We are using multiple enzymes and substrates in a combinatorial or iterative fashion, to generate microarrays of small molecules and screen them in high-throughput for biological activity. Ultimately, this will lead to an efficient platform for lead optimization which is a critical bottleneck in the drug discovery process.