2016 ACS-IRG Pilot Grant

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Project Title: A chemistry-based method for the discovery of irreversible inhibitors with anticancer activity

Abstract:

There is an urgent need to find novel natural products with anticancer properties as structural leads for the development of new cancer drugs. As half of all anticancer drugs approved over the last 30 years are natural products or natural product derivatives, the decision to direct our efforts in cancer drug discovery toward natural sources is reasonable. There are enormous opportunities to discover new bacterial natural products, in particular, as DNA sequencing efforts over the past 10 years have revealed numerous biosynthetic gene clusters, called "orphan" gene clusters, for which no compound has been found. However, the field of natural products research is plagued by the narrow-minded application of decades-old methods that are of limited value in realizing the full potential of bacterial genomes. The current proposal describes the development of an entirely new method for natural products research that facilitates the discovery of enzyme inhibitors that have evolved to covalently bind to their cellular targets. These irreversible inhibitors often target enzymes involved in the initiation and progression of cancer. For instance, several natural products or natural product derivatives that are FDA-approved (e.g. carfilzomib) or in clinical trials (e.g. marizomib or salinosporamide A, ONX-0912) are irreversible proteasome inhibitors developed for the treatment of multiple myeloma. Irreversible kinase inhibitors such as afatinib, ibrutinib, and osimertinib, which were designed to mimic the structure of ATP, are covalent drugs approved for the treatment of mantle cell lymphoma, chronic lymphocytic leukemia, and non-small-cell lung carcinoma. The method uses highly-visible thiol probes that mimic the nucleophilic amino acid residues of key cellular enzymes and are capable of labeling irreversible inhibitors in a crude extract. Though the method is still in its infancy, the probes have been shown to cleanly label well-established inhibitors that have been developed or are currently being developed into anticancer agents. In addition, the method has been demonstrated to work in crude bacterial extracts, efficiently and selectively labeling the proteasome inhibitors salinosporamide A and eponemycin and the kinase inhibitor neolymphostin A. Our overarching aim is now to apply this method toward the discovery of new irreversible inhibitors that target known and unknown cellular enzymes relevant to cancer chemotherapy.