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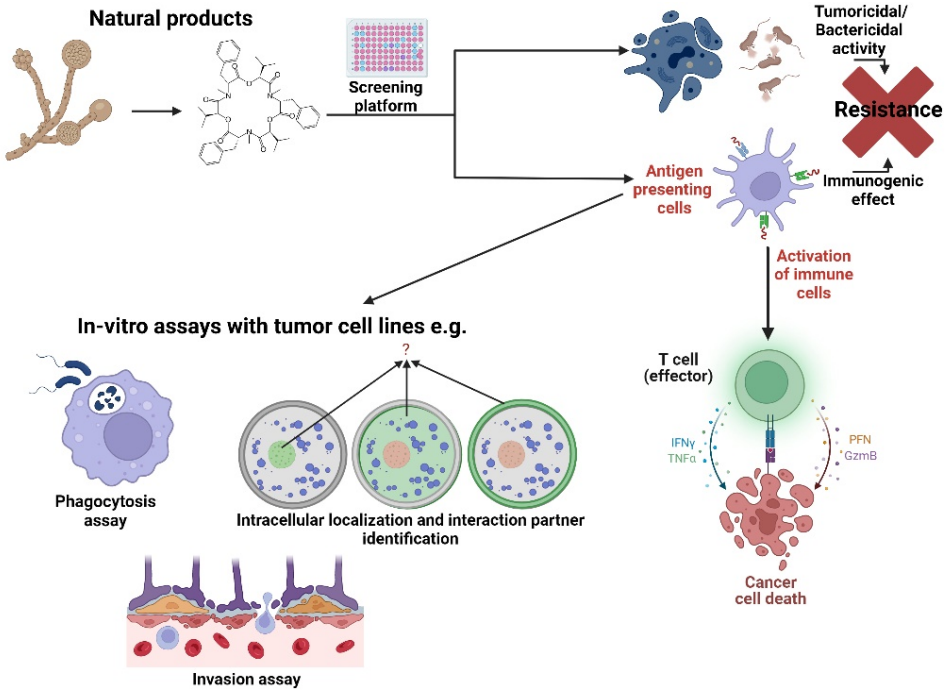
Elucidation of the mechanisms of action of immune-activating HDAC inhibitors and natural products for the development of new therapeutic approaches against chemoresistant tumor cells and bacterial pathogens



Description: A major roadblock in the treatment of cancer and infectious diseases is the emergence of resistance against cytostatic drugs and antibiotics. The goal of this study is to functionally analyze novel lead structures derived from natural products that exhibit cell autonomous toxicity against cancers or bacterial pathogens as well as the ability to alter immune effector activities. Previous work by members of the RTG 2158 suggest that the genetic deletion of specific Histone Deacetylases (HDACs) in tumor cells induces upregulation of tumor antagonizing gene (TAG) expression which in turn leads to recruitment of professional antigen presenting cells (APCs) to the tumor microenvironment and destruction of tumor cells. The multi-dimensional effect of immune activation and tumoricidal and/or bactericidal capacity combines in one compound considerably minimizes the chance of resistance development. Several potential candidate compounds have been identified in previous work within the RTG 2158 that not only activate professional APCs but also are cytotoxic to tumor cell line and/or are bactericidal. Aside from additional screening, the focus of this effort will be on elucidating the molecular and cellular processes behind these specified multifunctional natural compounds' immune stimulating ability as well as the optimization of lead structures.

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