Exploring the Cancer Stem Cell Hypothesis Using a Probe for ALDH1A1

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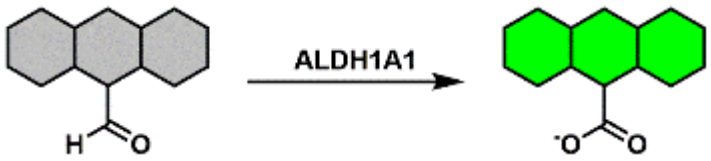
The human aldehyde dehydrogenase (ALDH) family consists of 19 isoforms which catalyze the oxidation of aldehydes to carboxylic acids. They play important roles ranging from metabolizing toxic aldehydes to producing vital carboxylic acids. Consequently, certain isoforms are upregulated in stem cells. Additionally, there is a strong correlation between elevated ALDH levels and poor prognosis in cancer leading many to consider ALDH (especially ALDH1A1) to be a biomarker for cancer stem cells (CSCs). We aim to exploit the enzymatic activity of ALDH1A1 to develop ALDH-based fluorescent probes for CSC detection, the first step towards therapeutic development. Early progress has demonstrated the feasibility of isoform specificity as well as capabilities for live cell and live animal imaging. In the interest of better sensitivity in vivo, selectivity for CSCs over healthy stem cells, and specificity for other isoforms, we are continuing to develop and test new probes for ALDH. In the end, we aim to use these tools and others developed in our lab to noninvasively study CSCs in the CSC niche.



Generation and Screening of a Lanthipeptide Library for Inhibitors of the p6/UEV Protein-protein Interaction

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Macrocyclic peptides are great scaffolds for protein surface recognition and inhibition of protein-protein interactions (PPIs) with ring structures mimicking the native ligands. We utilized a promiscuous lanthipeptide synthetase ProcM to generate a genetically encoded library of 10^6 lanthipeptides in *Escherichia coli*. This plasmid-encoded library was coupled to a bacterial reverse two-hybrid system (RTHS) for the protein-protein interaction (PPI) between the HIV p6 protein and the UEV domain of the human TSG101 protein, a PPI essential for the budding of HIV from infected cells. Using this method, we identified an inhibitor XY3-3 and verified the activity both *in vitro* and in cell-based virus-like particle budding assays. This study showed the successful generation of a large peptide library using lanthipeptide biosynthetic machinery for discovery of new biological activities, demonstrating the possibilities of the enzymes that produce this class of natural product.

34