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Comparison of Drug Sensitivity Profiles of Various NEN Spheroids

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BACKGROUND: Neuroendocrine neoplasms (NENs) are rare cancers that arise from neuroendocrine cells. NENs are classified as well-differentiated neuroendocrine tumors (NETs) and poorly-differentiated neuroendocrine carcinomas (NECs). Small bowel NETs (SBNETs) and pancreatic NETs (PNETs) are generally slow-growing but commonly metastasize to the liver and can become aggressive cancers. Little is known about the drug sensitivity profile of SBNETs, PNETs and NECs due to the lack of cellular and animal models of these malignancies. Recently, we have developed a general protocol to culture NET and NEC cells from patient tumors as patient-derived spheroids (PDS) for drug screens and showed that they express NEN markers. In this study, we compare the drug sensitivity profile of SBNET, PNET, and NEC spheroids in order to identify specific classes of inhibitors for each of these categories of NENs.

METHODS: We used 11 SBNET, 3 PNET, and 2 NEC PDS cultures in a systematic drug screen where each PDS line was tested against a panel of 175 compounds consisting of 147 FDA-approved anti-cancer drugs and 28 other compounds. We identified common and unique sets of inhibitors targeting specific NEN spheroid subgroups.

RESULTS: Our systematic drug screens identified 21, 35, and 67 drugs that can inhibit SBNET, PNET, and NEC spheroid growth, respectively. All 3 categories of spheroids are highly sensitive to proteasome, histone deacetylase, and tyrosine kinase inhibitors. Additionally, SBNET spheroids were sensitive to a larger number of topoisomerase inhibitors, while PNET spheroids were predominantly sensitive to PI3K and mTOR inhibitors. NEC spheroids were more sensitive to

antineoplastic compounds.

CONCLUSION: Our NEN patient-derived spheroid drug testing approach allows us to compare the drug sensitivity profiles of different NEN spheroids and better understand molecular pathways for therapeutic applications. These PDS cultures are a valuable model for NEN and can facilitate the process of drug discovery.

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