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A Systematic Workflow to Identify Anti-cancer Drugs Targeting Small BowelNeuroendocrine Tumors and Neuroendocrine Carcinomas

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BACKGROUND: The incidence of neuroendocrine tumors from the small bowel (SBNETs) has increased markedly over the past several decades. Many patients with these tumors present with metastatic disease, and research into new treatment options for these tumors has been hindered by the limited number of SBNET cell lines and in vivo models available for drug testing. The availability of resected patient tumors is a valuable resource of NET cells and could serve as a new model for preclinical studies. Here, we established a systematic method to culture Grade 1, 2, and 3 (G1/G2, G3) patient-derived SBNETs and neuroendocrine carcinomas (NECs) as spheroids for testing against a library of 175 compounds.

METHODS: Surgically resected SBNETs and patient-derived xenograft (PDX) NECs were processed, cultured as tumor spheroids, characterized for NET markers, and tested for sensitivity to 175 compounds. A comparison of drug sensitivity profiles of G1/G2 to G3 NET and NEC spheroids was performed.

RESULTS: Drug screening data from SBNET and NEC spheroids demonstrated high sensitivity to inhibitors targeting histones deacetylases, tyrosine kinases, topoisomerases, and components of the proteasome. Twenty-one drugs were effective at inhibiting growth of G1/G2 spheroids >50% whereas 59 drugs inhibited G3 spheroids >50% (Table 1). Comparison of the drug sensitivity data of G1/G2 to G3 revealed that the high-grade tumor spheroids are more sensitive to a broader range of antineoplastic agents than spheroids from G1/G2 tumors. The anti-tumor effects of the top 2 drug candidates were confirmed in PDX models.

CONCLUSION: We developed a systematic strategy to culture patient SBNETs and NECs as spheroids and perform drug screening. SBNET spheroids from G1/G2 tumors showed sensitivity to mainly 4 classes of anti-cancer drugs whereas G3 tumor spheroids displayed sensitivity to a variety of anti-cancer drugs. Together these in vitro and in vivo preclinical models identified new potential FDA-approved therapies for SBNETs and NECs.

Table 1. Categories of drugs inhibiting over 50% of G1, G2 and G3 spheroid growth

Categories	Number of drugs	G1/G2 spheroids sensitive drugs (n=10)	G3 spheroids sensitive drugs (n=3)
Antineoplastic	60	2	20
Tyrosine kinase inhibitors	27	3	7
mTOR/PI3K inhibitors	13	1	5
Topoisomerase inhibitors	11	7	10
HDAC inhibitors	6	3	5
PARP inhibitors	5	0	2
MAPK inhibitors	5	0	3
Anti-estrogen therapy 4 0 0	4	0	0
CDK inhibitors	4	1	3
Proteasome inhibitors	3	3	3
Hedghog inhibitors	2	0	0
Antibacterial	2	0	0
IDH2 inhibitors	2	0	0
Antiviral	1	0	0
Others	10	1	1
Unknown	20	0	0

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