Patient-Derived Organoids and their Potential for Precision Medicine in Neuroendocrine Tumors

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Background

Neuroendocrine tumors (NETs) are a heterogeneous group of malignant neoplasms arising from neuroendocrine cells distributed throughout the body. The most common sites of NETs are the gastrointestinal tract, pancreas and lungs. The clinical management of NETs is not standardized, with few FDA-approved therapies[1]. Moreover, drug development has been challenging for NETs due to limited pre-clinical models. To address this unmet need, the NCI Natural History Study of Children and Adults with Neuroendocrine Neoplasms (NCT03739827 and NCT05237934) aims to develop preclinical models, such as *in vitro* 3-dimentional tissue organoids, to develop more personalized therapies for NET patients, as have been used in other cancers including melanoma[2].

Methods

From February 2020 – July 2022, 23 surgical specimens were collected for the development of patient-derived organoids. We selected 5 NET organoids (NET16, NET17, NET18, NET21, and NET22) to test the activity of select drugs: dovitinib (VEGFR inhibitor), vistusertib (mTOR inhibitor), entinostat (histone deacetylase inhibitor), cobimetinib (mitogen-activated protein kinase 1 inhibitor) and TAK243 (ubiquitin activating enzyme inhibitor). NET21 was used for chromogranin and synaptophysin staining.

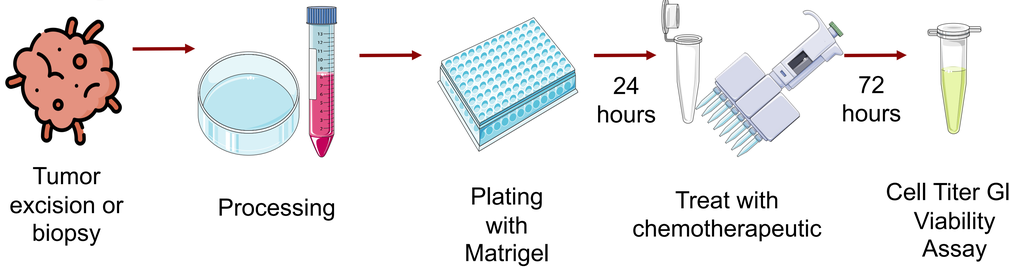

Table 1: Patient characteristics used for patient derived organoids

Patient	Age	Gender	Primary Site	PDO Tumor Site	Grade	Treatment History
NET16	72	Male	Colon	Ileocecal Metastasis	Grade 1 (Ki67<3%)	No prior treatment
NET17	36	Female	Small Bowel	Liver Metastasis	Grade 2 (Ki67=3-4%)	No prior treatment
NET18	66	Male	Ileocolic	Liver Metastasis	Grade 2 (Ki67=3%)	Lanreotide, radioembolization
NET21	59	Male	Pancreas	Liver Metastasis	Grade 1 (Ki67<3%)	Octreotide and Sandostatin
NET22	47	Female	Small bowel	Liver Metastasis	Grade 1 (Ki67<3%)	Octreotide and Lanreotide

Patient-Derived Organoid Imaging and Immunofluorescence

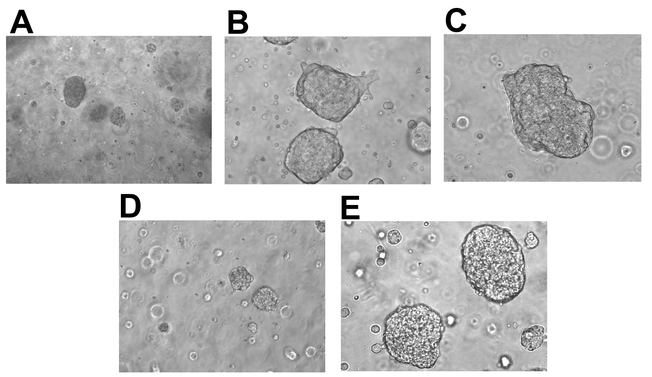

Figure 1: Patient Derived Organoid images from NET 16 (A), NET17 (B), NET18 (C), NET21 (D), and NET22 (E). All P0 and 40x.

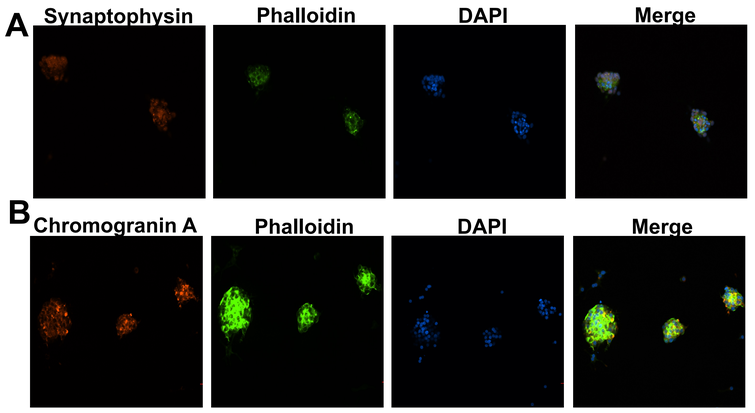

Figure 2: Patient Derived Organoid NET21 positive neuroendocrine marker (Synaptophysin and Chromogranin) staining.

Patient-Derived Organoid Drug Assays

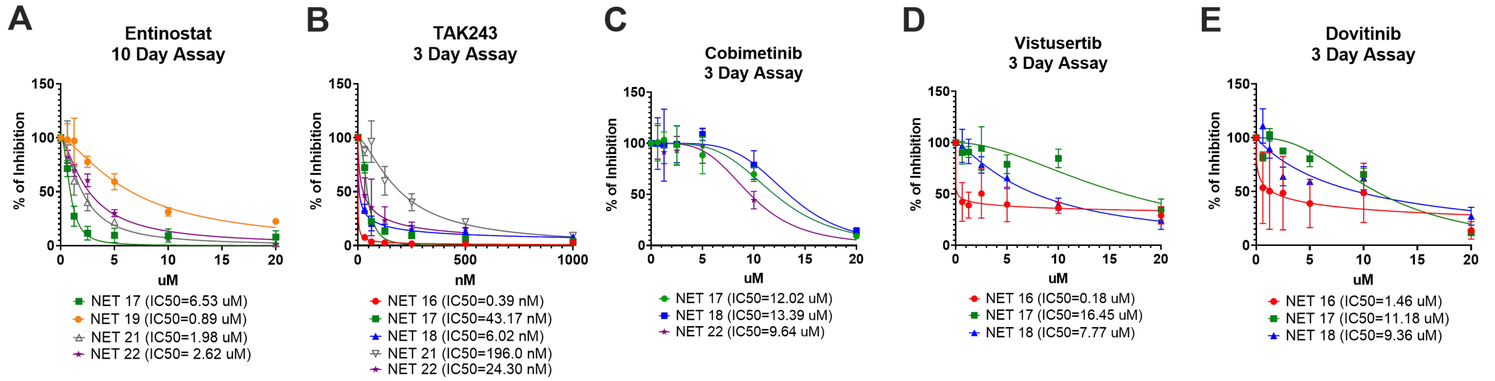

Figure 3: Drug assays showing efficacy in Entinostat (A), TAK243 (B), Cobimetinib (C) and modest activity in Vistusertib (D) and Dovitinib (E) in P0 NETs 16, 17, 18, 19, 21, and 22.

Conclusion

We have developed an assay for in vitro drug testing in well-differentiated patient-derived NET organoids that will allow for further, large scale drug screening to help predict patient drug responses. Tumor heterogeneity may be contributing to the differences seen in the drug response between the three NET organoids and requires further evaluation. Replication of these studies in a larger subset of patient samples and drug combination studies will be important for the advancement of therapeutics in NETs.

References

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2. Porcelli L, Di Fonte R, Pierri CL, et al. BRAFV600E;K601Q metastatic melanoma patient-derived organoids and docking analysis to predict the response to targeted therapy. Pharmacol Res. 2022;182:106323. doi:10.1016/j.phrs.2022.106323

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