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Patient-Derived Organoids as an In Vitro Model of Neuroendocrine Tumors

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Background: Despite the major clinical advances made in treating neuroendocrine tumors (NETs) over the past decade, there remains a dearth of methods by which NETs can be studied in the laboratory. In particular, existing NET cell lines are believed to poorly represent NET biology and behavior. The advancement of 3D organoid culture over the past few years has opened the door to the use of organoids as models for recapitulating and experimenting on tumor properties in the setting of the laboratory.

Methods: Surgically resected NET samples were collected by the Stanford Tissue Bank from consented patients who had not undergone neoadjuvant therapy. Primary tissue was minced, then suspended in collagen for culture in the double-dish Air-Liquid Interface format. The primary tissue was cultured in supplemented basal medium, including the growth factors Wnt, EGF, Noggin, and R-Spondin. Media was changed 1-2 times per week, and cultures were passaged around once a month, according to the growth rate of individual cultures. Organoid samples were collected for histological analysis by hematoxylin and eosin staining, as well as NET-specific chromogranin A and synaptophysin staining.

Results: Thirteen NET samples were successfully initiated as expanding organoid cultures. Of the thirteen NETs, 9 originated from the pancreas, 2 from the lung, one from the small intestine, and one from the stomach. The NET organoids grew relatively slowly, compared to adenocarcinoma samples, in accordance with the indolent nature of NETs *in vivo*. While some of the slowest-growing samples began dying after 1-2 passages, robust cultures have survived up to 6 passages and continue to expand.

Conclusion: Patient-derived NET organoids offer the potential for establishing “lines” that more accurately recapitulate the biology and behavior of NETs. Further characterization of such cultures is necessary and may offer the opportunity to better understand NET biology and effect treatment in pre-clinical models.