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Development of innovative in vitro and in vivo patient-derived cancer models for translational studies in G1/G2 gastroenteropancreatic neuroendocrine tumors

Yi Liu[1], Jessica Maxwell[2], Daniel Halperin[1], Arvind Dasari[1], Scott Kopetz[1], Xiangsheng Zuo[1], James C. Yao[1]

[1]Department of Gastrointestinal Medical Oncology, [2] Department of Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

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Background

Well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs) grow slowly but are nonetheless lethal when advanced. Despite progress, effective systemic treatments for GEP-NETs remain limited. A key barrier is the scarcity of clinically relevant models that accurately reflect human GEP-NET biology. To address this important gap.

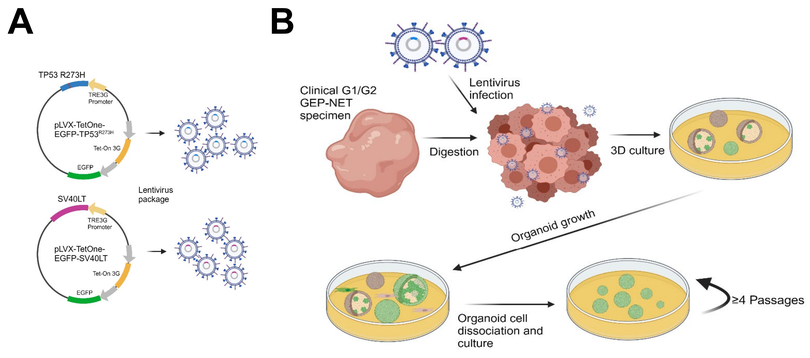
Challenges of generating human G1/G2 GEP-NETs models

1. 2D cell line models are not representative for the morphology of original G1/G2 GEP-NET; Several GEP-NET cell lines, such as BON1 and QGP-1, exhibiting NEC characteristics (e.g., TP53/RB1 mutations, high Ki67 rate).
2. 3D models: Failure of developing patient derived organoids (PDOs) of G1/G2 GEP-NETs capable of long-term passage on >150 attempts (Kawasaki et. al. Cell, 2020; Dayton et. al. Cancer Cell, 2023).
3. PDX models: no models available.

Genomic spectrum of NEN

4. TP53 and Rb alterations are frequent in poorly differentiated NEC, but rare in well-differentiated NET
5. Well-differentiated NET can acquire TP53 mutations when transforming to poorly differentiated NEC
6. Mutant p53 abolishes tumor suppressor capacities and confers gain-of-function; SV40 T antigen inactivates p53 and Rb1 and was used for NEN GEMM models

Experimental design

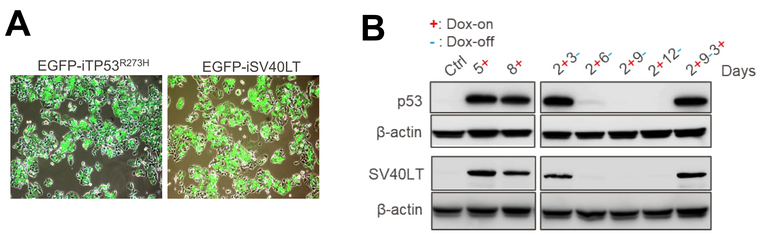


Goals

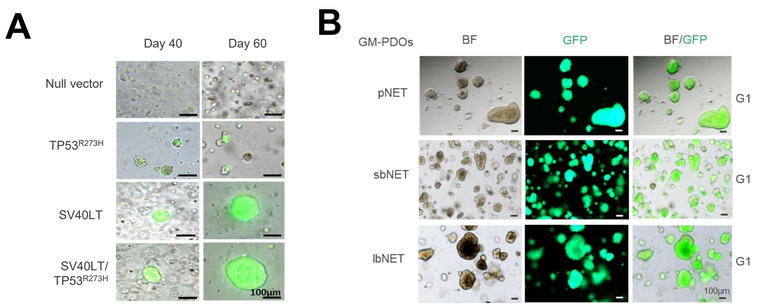
- Introduce reversible modifications to drive proliferation and establish model
- Revert to original state to study biology and test new therapy

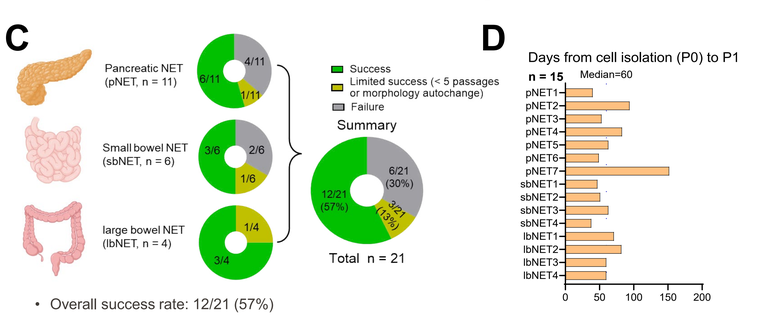
Results

The expression of the genes is doxycycline controllable

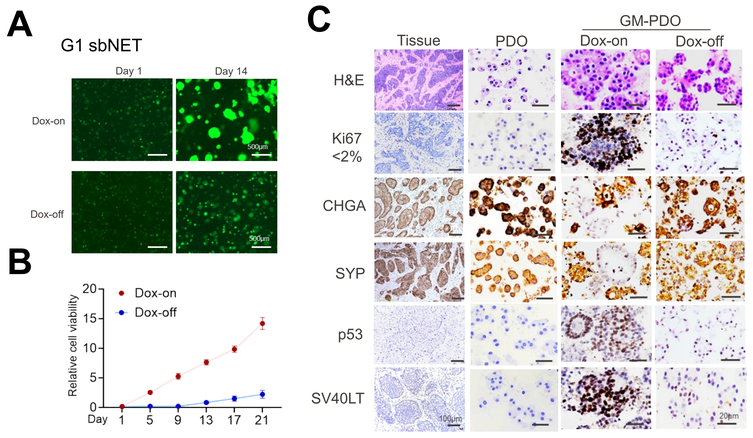


Generation of G1/G2 GEP-NET GM-PDOs

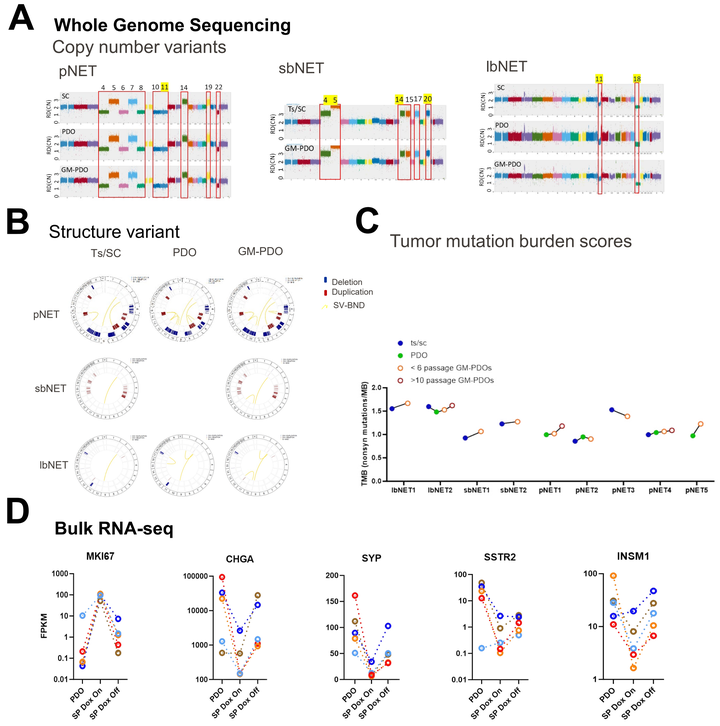




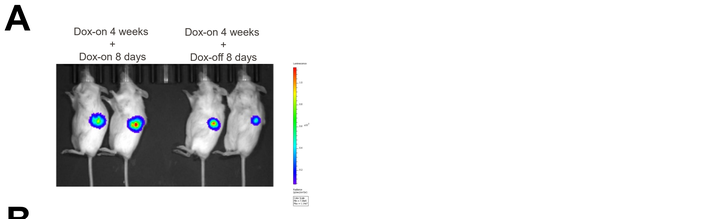
Phenotype of GM-PDOs recapitulates original G1/G2 GEP-NET



Multi-omic sequencing characterization of GM-PDO



GM-PDX resembles the original G1/G2 GEP-NET



Conclusion

Innovative in vitro and in vivo patient-derived cancer models that could recapitulate the genomic and biological features of human G1/G2 GEP-NETs were successfully developed for the first time. These models yield unique materials enabling translational studies in GEP-NETs.