Precision Medicine for mNETs: Update on Organoid Research

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6 March 2020
DISCLOSURES

- Trisalus Life Sciences- Scientific Advisory Board
- Grant Funding
  - NIH
  - Veterans Administration
  - Society of Interventional Oncology
  - Society of Interventional Radiology
  - RSNA
NETs: A Growing Health Problem

Increasing Incidence of NET

Metastatic Disease is Common

NET incidence per 100,000 has INCREASED FROM 1.7 IN 1980-1989 TO 14 IN 2019

Adapted from https://gicancer.org.au/cancer/neuroendocrine-tumours/
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Therapeutic Targeting of mNETs: Challenges

- Unrepresentative Samples
- Limited Biobanks
- Suboptimal Model Systems
Penn mNET Biopsy Protocol

Observational Clinical Trial:
Biopsy of Liver mNETs at time of TAE/TACE

- Genetic Sequencing
- Genome Mapping
- Metabolomic Profiling
- Model Generation
MODEL GENERATION: ORGANOIDS

Tumor Organoids Provide Unique Cancer Models

- Self-organizing 3D structures grown in vitro
- Recapitulate the architecture and function of the parent human tumor
- Diverse applications
  - Study of representative cancer biology
  - Precision medicine
    - Identify optimal therapy for each patient

Schematic of Tumor Organoid

Adapted Tuveson Science 2019
Methods for organoid generation from mNET biopsy samples are not well established.
mNET ORGANOID CREATION: PROGRESS

Optimized Culture Conditions

mNET Patient

Biopsy

Relative adherence (75th percentile)

Growth

Patient 11
Patient 16

Patient 11
Patient 16
**Precision Medicine**

Personalized therapy against specific vulnerabilities in each patient’s cancer

**Key Components**
- Consistent acquisition of tissue samples
- Safety & compatibility with current clinical workflow
- Robust patient-derived models (organoids)

*The right drug for the right patient*
PARADIGM

1. mNET Patient
2. Biopsy
3. Primary Culture (Organoids)
4. High throughput chemical screen
5. Putative targets
6. Clinical application
7. In vivo Expansion
### Precision Medicine: Patients 17 & 20

#### Biopsy

1. Cell isolation & expansion

2. Validation

3. Screen

#### 44 Hits that overlap

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<thead>
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<th>Product Name</th>
<th>Class</th>
<th>Catalog No.</th>
<th>Targets</th>
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<tbody>
<tr>
<td>Gemcitabine</td>
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<td>kinase</td>
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<td>S2622</td>
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<tr>
<td>GW9508</td>
<td>kinase</td>
<td>S8014</td>
<td>Epigenetic, HMG-CoA, MEK</td>
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<td>Atorvastatin</td>
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<td>S2077</td>
<td>Epigenetic, HMG-CoA, MEK</td>
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<td>Kras, PI3K</td>
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<tr>
<td>Cephalomannine</td>
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<td>S2408</td>
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#### 15 Hits unique to Patient 17 (M898)

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#### 8 Hits unique to Patient 20 (M2842)

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**Patient 17M**
Precision Medicine: Patients 17 & 20

Biopsy

Cell isolation & expansion

Validation

Screen

Normalized % Inhibition

FDA-Approved Drugs

Dasatinib
Vorinostat
Temsirolimus
Gemcitabine
Pemetrexed
Valpazinc
Pancrtaxinol
Doxorubicin
Mitomycin
Cisplatin
Sorafenib
Regorafenib

Patient 17P
Patient 17M
Patient 20

Other Malignancies

HCC

Patient 20
Precision Medicine: Patients 17 & 20

- Biopsy
- Cell isolation & expansion
- Validation
- Screen
Feasible to establish mNET organoid cultures from needle biopsy samples

Drug screening enables identification of existing, FDA-approved drugs on a patient-by-patient basis

Foundation for precision medicine approach to mNET
FUTURE DIRECTIONS: DEVELOPMENT FOR CLINICAL IMPLEMENTATION

1. Optimize culture of, and validate, *in vitro* (organoid) & *in vivo* models
FUTURE DIRECTIONS: DEVELOPMENT FOR CLINICAL IMPLEMENTATION

1. Optimize culture of, and validate, *in vitro* (organoid) models

2. Leverage models for precision medicine paradigm for patients with mNETs
ACKNOWLEDGEMENTS

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Stephen Hunt
James Chen

Stem Cell & Xenograft Core

Tony Secreto
Josh Glover

HT Screening Core

Sara Cherry
David Schultz

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