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Proposal for Finding Treatments for Liver Cancer Using Liver Organoids

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PROPOSAL FOR FINDING TREATMENTS FOR LIVER CANCER USING LIVER ORGANOIDS
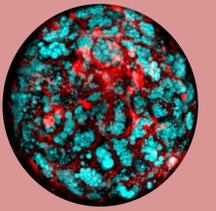
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What is an Organoid?

- An organoid is a three-dimensional model of an organ. Liver organoids can be made from induced pluripotent stem cells[7]

- These organ-like models have been used in the clinical setting for a few years Before organoids were created, two-dimensional *in vitro* cells and mouse models were the common modes of modeling cancer metastasis[6]

- Different types of organoids
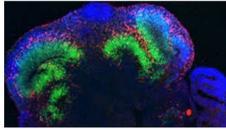
  (Fig. 1, Fig. 2, and Fig. 3)

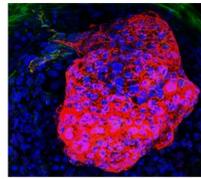**Figure 1:** immunofluorescent image of a brain organoid.[8] **Figure 2:** image of an intestinal organoid.[8] **Figure 3:** image of a heart organoid.[3]

Prevalence and Treatments

- Liver cancer is the fifth most common cancer found in men and the ninth most common found in women[4]

- In 2018 there were more than 840,000 new cases[5]

- Around 4% of people that are diagnosed with stage four liver cancer have a five-year survival rate[5]

- Common causes
  - Diabetes[2]
  - Cirrhosis[2]

- Chemotherapy treatments include cisplatin, doxorubicin, and oxaliplatin[1]

- Immunotherapy treatments include pembrolizumab (Keytruda) and nivolumab

- With both types of treatment the 5-year relative survival rates are low[1]
  - Localized cancer 31%
  - Regional 11%
  - Distant 2%

Specific Aim

- Find an effective model for treating liver cancer at all stages of growth by using tumor organoids

- Tumor organoids will be introduced to different treatments at varying dosages in order to measure the changes in tumor growth

- Hypothesis: Liver tumor organoids will be effective models for testing chemotherapy and immunotherapy drug effectiveness in treating liver cancer.

Potential Pitfalls

- Organoids are still relatively new concept in organ modeling

- Expenses can add up when growing and maintaining organ models

- Human models will require strict protocol for maintaining the organ-tike tissue

- Potential ethical problems associated with the use of human tissues in the lab

Potential Conclusions

1. The liver tumor organoids grown directly from patient tumors will be the more effective model for testing immunotherapy and chemotherapy drugs (Part A in Figure 4).

2. The healthy liver cells induced into cancerous cells could be a model for learning how cancer effects an individual and how an individual will respond to various treatments (Part B in Figure 4).

3. Neither cultured liver organoids will be a good model for understanding the mechanism of liver cancer, or how immunotherapy and chemotherapy drugs affect liver tissue in the human body

For liver tumor organoids to fit my hypothesis:

o Tumor regression would be seen in effective drug environments

o No onset of tumor growth seen in a treated, cultured organoid
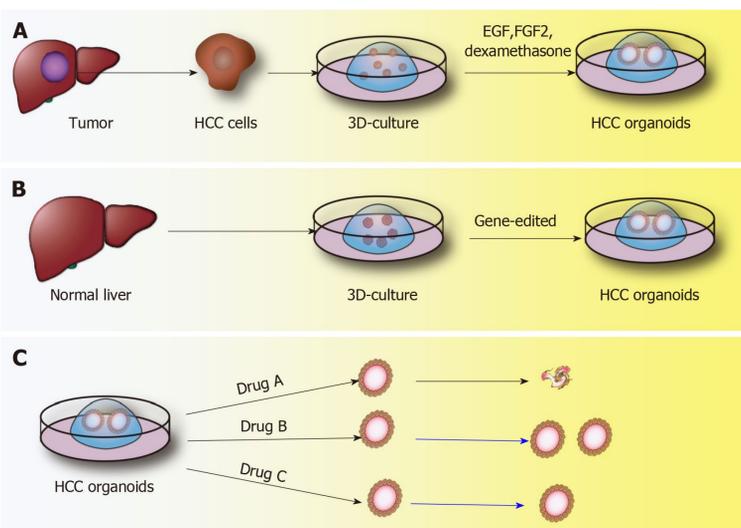
Methods

Figure 4: Methods of culturing liver cancer organoids[9]

A: Liver cancer cells are directly removed from a biopsied tumor sample.
B: Normal liver tissue organoids are being transformed into cancerous organoids by using gene editing.
C: Using liver organoids to observe liver cancer mechanisms and how liver cancer cells react to three different drugs.

• Patient liver tumor cells will be directly suspended in Matrigel. Growth factors will be added to the tumor cells, allowing them to mature in a 3-D shape (Fig. 4, part A)

  o Chemotherapy drugs at several different concentrations will be introduced
  o Immunotherapy drugs at several different concentrations will be introduced

• Healthy liver tissue will be added to the Matrigel. Gene editing will transform them into tumor organoids (Fig. 4, part B)

  o Chemotherapy drugs at several different concentrations will be introduced
  o Immunotherapy drugs at several different concentrations will be introduced

• Comparison of tumor differences between the different treatments and different growth protocols (Fig. 4, part C and Fig. 5)
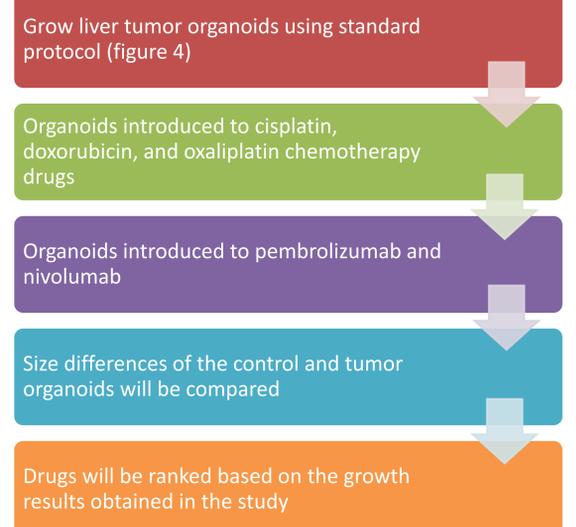
Grow liver tumor organoids using standard protocol (figure 4)

Organoids introduced to cisplatin, doxorubicin, and oxaliplatin chemotherapy drugs

Organoids introduced to pembrolizumab and nivolumab

Size differences of the control and tumor organoids will be compared

Drugs will be ranked based on the growth results obtained in the study

Figure 5: Methodology for this proposal.

Citations

[1]Bosch F, Ribes J, Díaz M, Cléries R. 2004. Primary liver cancer: Worldwide incidence and trends. Gastroenterology 127:S5-S16.
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[6]Skardal A, Devarasetty M, Rodman C, Atala A, Soker S. 2015. Liver-Tumor Hybrid Organoids for Modeling Tumor Growth and Drug Response In Vitro. Annals of Biomedical Engineering 43:2361-2373.
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