



## Team Progress Updates

### SU2C-Dutch Cancer Society Tumor Organoids Dream Team:

#### “A New Preclinical Model for Drug Sensitivity Analysis”



The promise of precision medicine lies in the ability of researchers to devise treatments that are specific to the genetic profile of individual patients and their tumors. However, predicting which drug or drug combination will be the most effective based on the genetic makeup of a tumor remains a challenge.

In order to investigate the consequences of all the DNA changes that contribute to cancer progression, and how those changes can be targeted by drugs, this Dream Team has developed a groundbreaking technology that allows tumor samples isolated from patients to be maintained and grown in a laboratory setting as “tumor organoids.”

Importantly, these tumor organoids will allow studies of sensitivity and resistance to a large number of anticancer drugs in the lab. The ultimate goal is to design new and more sophisticated clinical trials that test treatment regimens tailored to a patient's tumor. If successful, this Dream Team project has the potential to provide a true paradigm shift in our current approach to drug development, clinical trial design, and therapy, ultimately providing effective new targeted treatment options for cancer patients.

In work to date, the SU2C-Dutch Cancer Society Tumor Organoids Dream Team has:

#### **December 2018**

- The team continues to develop organoids bearing CRISPR-based manipulations to study the impact of specific oncogenes on tumor development and metastasis.
- The team has sequenced DNA and performed drug screening for colon cancer and pancreatic cancer organoids.
- The researchers have used their tumor organoids to establish new drugs or drug combinations either currently in clinical trials or being readied for trials.
- The team continues to build its “living biobank” of colon cancer, breast cancer, pancreatic cancer, esophageal adenocarcinoma, ovarian cancer, and head and neck cancer organoids.





## Team Progress Updates

### June 2018

- The team has continued to expand its organoid biobank, which now includes organoids from colon, breast, pancreatic, ovarian, head and neck, and esophageal cancer.
- The team used its colon cancer organoids to identify therapies that are effective in tumors with mutant RAS, a type of colon cancer that is more difficult to treat. In particular, the team found a triple drug combination that may be able to treat patients with a RAS mutation.
- The team has cultured tumor organoids with cancer-killing T cells. By developing these cultures, the team can perform studies to help illuminate how the cancer-killing effect of T cells can be maximized.
- The team has established 54 ovarian cancer organoid cultures. It is testing different drugs on these organoids to identify new treatments for ovarian cancer.
- The team has continued to develop CRISPR-manipulated organoids to understand the mechanism underlying the growth of cancers and identify potential approaches to eradicate them.

### December 2017

- Established a 'living biobank' consisting of over 80 colon cancer organoids, over 80 breast cancer organoids, over 40 pancreatic cancer organoids and over 30 esophageal adenocarcinoma organoids.
- Performed DNA sequencing and drug profiling of colon cancer organoids, with further characterization planned.
- Found that tamoxifen had similar effects on breast cancer organoids and on patients. This suggests that organoids can be used to predict whether a drug will be effective in patients.
- Developed organoids from fallopian tubes of patients. These organoids can be used to understand some of the ways by which ovarian cancer can develop.
- Developed liver cancer organoids. From studies with these organoids, they discovered that an ERK inhibitor may be used to treat liver cancer.

### June 2017

- Reached the target number of organoids for three different cancers: 80 for colon, 101 for breast, and 45 for pancreatic cancer.
- Created biobank of 30 organoids from esophageal cancer.



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- Tested 300 drugs that are either approved or in clinical trial to identify drugs that can be combined with EGFR-MEK inhibitors, against tumors with mutant K-Ras.

### **December 2016**

- Established more than 80 tumor organoids of the colon.
  - Working with the Wessels lab, the Team is developing an analytical approach for screening drug combinations.
  - Using gene-editing technology, CRISPR-Cas9, to introduce gene mutation combinations in colon organoid cultures, the Team has identified an exact combination of mutations that result in metastasis. These data are being prepared for publication.
- Established a biobank of 101 tumor organoids of the breast that have been validated to mimic the histological features of their original tumors.
- Established 33 tumor organoids of the pancreas.

### **June 2016**

- Completed biobanks of colon cancer and breast cancer tumor organoids with 80 or more organoids in each.
- Discovered that mutant K-RAS colon tumor organoids are very sensitive to a triple combination of an EGRF inhibitor, a MEK inhibitor, and an inhibitor of a molecule called BclXL.
- Determined that within individual tumors there can be significant differences (heterogeneity) and that this may mean that drug-resistant cells exist within a tumor even before treatment begins.

### **December 2015**

- Expanded colon cancer tumor organoid biobank to 86 tumor organoids, many of which are paired with normal colon tissue for comparison. Nine colon cancer metastases are included in the biobank.
- Established good reproducibility in the initial drug screening work.
- Launched drug screening and genetic characterization at the required scale. The first results are expected in the next 6 months.



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### June 2015

- Expanded the biobank to 67 normal-tumor pairs of organoids from colon and 22 pairs from pancreas, with a high success rate in growing colon and pancreas organoids and a steady supply of samples from collaborating hospitals.
- Successfully established the process for growing prostate organoids from lymph node metastases and report three samples in the biobank.
- Screened a panel of 83 drugs and found a range of responses– some organoids respond very well to certain drugs and others respond poorly – and are working now to understand the biological reason for the individual tumor organoid response to specific drugs.

### December 2014

- Established the infrastructure for building the living biobank.
- Established a >95% success rate for growing colon cancer organoids and have a bank of 22 colon cancer organoids, from 20 patients, along with healthy colon tissue from the same patients for comparison.
- Established the method for growing pancreas cancer organoids, and have successfully established 10 out of 11 pancreas cancer organoids.
- Optimized the method for growing prostate cancer organoids, although the success rate is lower than colon or pancreas cancer.
- Established that tumor organoids contain the genetic features and diversity of the original tumor.
- Initiated tests for anti-cancer drug responses using tumor organoids.