Patient-derived Organoids of RAS/RAF Wild-type Metastatic Right Colon Cancer to Test the Sensitivity and Clinical Consistency of Combined Treatment of Cetuximab

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Informed Consent Form

Informed part

You are invited to participate in a scientific research project called " Patient-derived Organoids of RAS/RAF Wild-type Metastatic Right Colon Cancer to Test the Sensitivity and Clinical Consistency of Combined Treatment of Cetuximab" initiated by D1 Medical Technology (Shanghai) Co., Ltd and the Department of Colorectal Surgery, Fudan University Cancer Hospital. The project is introduced as follows:

1. Research background

Colorectal cancer is one of the most common malignant tumors worldwide. Its morbidity and mortality rate ranks third among all tumors. In China, with the improvement of people's economic conditions, changes in living habits, and dietary patterns, the incidence of colorectal cancer is increasing year by year. The early symptoms of colorectal cancer are insidious. Although the level of diagnosis and treatment of colorectal cancer continues to improve, about 20% of patients are diagnosed with metastatic colorectal cancer. In recent years, targeted drugs have provided new treatment options for metastatic colorectal cancer, opening a chapter in individualized treatment. EGFR monoclonal antibody (cetuximab) single agent can benefit KRAS wild-type metastatic colorectal cancer patients with a survival benefit of 4.6 months. However, its objective effective rate is only 13-17%. At present, there is still a lack of reliable indicators that can accurately predict the sensitivity of EFGR monoclonal antibody treatment in clinical. Continuously exploring and revealing new drug resistance mechanisms of EGFR monoclonal antibodies, finding effective methods for predicting efficacy, and determining potential targets for effective intervention are essential strategies to improve the effectiveness of targeted therapy for colorectal cancer.

The organoid model (patient-derived organoid model, PDO model) is established based on organoids. In 2009, Hans Clevers and others discovered that Lgr5-positive stem cells located in crypts in the intestine could be cultured into organoids in vitro. A study published in Science in 2018 revealed the predictive value of the PDO model in the treatment of metastatic gastrointestinal tumors. The results showed that organoids maintain a high degree of consistency with the source tumor tissue in histology, molecular level, and function. When using PDO models to predict patient’s responses to drugs, the overall sensitivity is 100%. The specificity is 93%, the positive predictive value is 88%, and the negative predictive value is 100%. In 2019, our group tried to explore the value of the PDO model in predicting the efficacy of neoadjuvant radiotherapy and chemotherapy for rectal cancer. We found the overall sensitivity is 78.1%, and the specificity is 84.43%. Our work

is published on Cell Stem Cell. These two studies provide direct evidence of the PDO models in the screening of individualized precision therapy drugs.

It has become a consensus that the left and right RAS/RAF wild-type colon cancers have different sensitivities to the clinically targeted drug cetuximab. However, there are still some patients with the right colon cancer who are sensitive to cetuximab. It urgent to screen out RAS/RAF wild-type metastatic right colon cancer patients suitable for cetuximab. We will establish organoids from the pre-treatment biopsy specimens from patients with RAS/RAF wild-type metastatic right colon cancer. Organoids will be exposed to the chemotherapy drugs or chemotherapy drugs combined with cetuximab used for each patient. The sensitivity of chemotherapy drugs or combined cetuximab will be tested in the organoid model. The purpose of this study is to evaluate the consistency and accuracy of a PDO model of colon cancer to predict the clinical efficacy of combined treatment of cetuximab, which to formulate the best therapy regimen for each given patient.

2. What do you need to do if you participate in this research

This study will carry out in the Fudan University Cancer Hospital, and it has been reviewed and approved by the hospital ethics committee. We expect that 80 subjects will participate voluntarily, and the duration of this study is from April 2021 to December 2023. If you agree to participate in this scientific research project, we will number each subject, establish a medical record file, and collect tumor tissue samples from the subject. Details are as follows:

"Patient tissue specimen collection": Due to the needs of clinical diagnosis or treatment, you need to perform some surgical operations or needle biopsy. We will collect the remaining tissues except for routine clinical-pathological examinations for this study.

In addition, after the operation, you should follow the requirements of this study plan, cooperate with the investigator, and perform a series of necessary drug treatments, laboratory tests, and imaging examinations as required, so that the clinical investigator can make a correct evaluation of your disease development

3. The possible benefits of participating in this study

If the doctor judges that you can join this study, the researchers will conduct in vitro organoid culture of the tumor tissue. The drug sensitivities results on organoids will compare with the sensitivity of your clinical treatment. In addition, the information obtained through the research may help improve the treatment of this disease, which may benefit other subjects with similar conditions to yours. It may not benefit you personally who participated in the research.

4. Adverse reactions, risks, and risk prevention measures that may occur when participating in this study

Your participation in this study bases on the premise that your rights and interests will not be harmed, nor will it interfere with your routine clinical treatment. Therefore, there will be no direct or indirect adverse reactions and risks caused by this study. "Patient tissue specimen collection" will be performed by professionals such as Surgeons. We only collect some tissue specimens leftover from clinical-pathological examinations, and there will be no direct or indirect adverse reactions and risks caused by this study.

5. About the cost

The tumor tissue organoid culture in this research is free. We recommend you cooperate with your attending doctor to carry out drug treatments, laboratory tests, and imaging examinations so that clinical researchers can make a correct evaluation of the development of your condition. Besides, whether and when laboratory tests and imaging examinations will carry out are determined by your attending doctor. They will make the decision based on your clinical treatment decisions and or your condition. There are no additional checks. You are responsible for all inspection, medication, and treatment fees. There are no transportation allowances for participating in this study.

6. Subject's privacy and confidentiality

If you decide to participate in this research, your participation and personal information will be kept confidential. Information that can identify you will not be disclosed to members other than the research team unless we have your permission. Your file will be store in a safe place and is only available to researchers. The research will carry out under regulations. The government management department or the ethics review committee members have the right to check your personal information. When the results of this research are published, your personal information will not be disclosed.

7. Termination of participation in research

Whether to participate in this study is entirely up to your volition. You can choose not to participate in this study or notify the investigator to withdraw from the study at any time. If so, your data will be eliminated from the study results without affecting your medical treatment and rights. In addition, your participation in this research may be terminated due to the following reasons:

1). You have not followed the doctor's orders.

2). Due to various reasons, your tumor tissue sample is incomplete.

8. Ethics Committee

If you have any questions about this research or experience any discomfort or injury during the study, you can contact Dr. Yaqi Li at 18121299615 or the nurse Zhuzhu Qian at 18121299246. If you have questions about ethics during the research process, you can

contact the Ethics Committee Office at 2nd Floor, Building 2, No. 270, Dongan Road, Xuhui District, Shanghai; Contact: Teacher Zhang, Tel: 021-64175590-88503.

Consent Part

I have read this informed consent form.

I have the opportunity to ask questions, and all questions have been answered.

I understand that participation in this study is entirely voluntary.

I know that my samples and all information will be confidential within the scope permitted by law.

I can choose to withdraw from this study at any time, and any of my medical treatment and rights will not be affected.

I know that signing does not mean that any fees, due diligence, and drug costs can be waived.

I will get a signed and dated copy of the informed consent form.

Signature of the subject or guardian: _____

Signature of the researcher: _____

Date: _____