Text box 1. The banking of gut organoids of patients with Cystic Fibrosis (CF) for precision medicine

Background on organoid technology and Cystic Fibrosis

Cystic Fibrosis (CF) is a severe hereditary disease that leads to predominantly lung and intestinal problems and results in a limited life expectancy. Previously only symptomatic treatment was available. However, recently novel drugs have been developed that target the underlying cause of the disease: a defect in the cystic fibrosis transmembrane conductance regulator (CFTR) protein that affects the ion channels of cells and is caused by ~2000 different mutations in the related *CFTR* gene [1,2]. Nevertheless, it remains hard to predict which patients benefit from these costly drugs and there are numerous patients with rare mutations still awaiting proper treatment options. Organoid technology can aid in developing treatment strategies for all patients with CF [1].

Rectal biopsies of patients can be transformed into gut organoids in a dish. Because of their genetic and functional resemblance to the individual patient, they constitute a strikingly accurate and personalized model for disease. This allows for studying the disease mechanisms as well as personalized and large-scale drug testing and development with the use of a so-called swelling or CFTR assay. If a treatment is effective the improved function of the CFTR protein causes the transportation of ions and fluid into the lumen which results in swelling of the mini-gut. The CFTR assay was developed by Dutch researchers [1,3].

Here, we will outline a hypothetical scenario of an 'organoid journey' to illustrate how rectal biopsies of patients with CF can be transformed into gut organoids, acquire different meanings and value, become of interest to multiple parties, and move through gift and market discourses. Although the scenario is fictitious, it reflects a potential real-world journey [4].

Gut organoids: from patient to biobank

Jasper is a 25-year old Dutch patient with CF. Recently, despite symptomatic treatment such as physiotherapy exercises and antibiotics, his lung function is declining which affects his ability to study and exercise. During his periodical out-patient visit to the CF center his treating physician mentions the possibility to participate in a new study called the 'Rainbow project' in which rectal biopsies of patients with rare mutations are used to generate mini-guts and test several existing and novel drugs [5]. If there is a positive response in the patient's mini-gut, the drug will be tested in the patient. Jasper is positive about participation, because this may open up new avenues for treatments.

During a follow-up conversation with the research nurse the details of the rectal biopsy procedure and the project are elaborated on and Jasper's consent is sought for participation. Simultaneously, the research nurse asks consent for storage in the Hubrecht Organoid Technology (HUB) biobank [6]. She explains that biobank storage enables longitudinal use of the mini-guts for CF research as well as drug testing and development. Jasper receives a detailed patient information letter on the conditions for biobank storage [4]. These include the notification that the biobank (a non-profit organization) may

grant access to commercial parties. Donors cannot claim any ownership in nor share in any future financial benefits flowing from the products that these companies develop. Jasper decides to consent to biobank storage, even though he finds it uncomfortable that his mini-guts can be endlessly used by others without his knowledge and he is ambiguous about commercial use. However, he considers it to be a waste if his mini-guts are destroyed after closure of the Rainbow project and he trusts his physician.

After Jasper's consent his tissue is procured through a rectal biopsy procedure in his treating hospital. The specimen is coded and transported to the laboratory of the principal investigator of the Rainbow Project. A postdoctoral researcher isolates adult stem cells from the specimen and puts these into a petri dish containing the right culture medium. Within 7 days the stem cells start to grow and expand and self-organize into 3D intestinal structures: gut organoids. These gut organoids are stored in the freezer until the drug testing starts. A couple of months later the inclusion is complete and the researcher tests ~900 FDA approved drugs in high-throughput plates on the gut organoids of over 120 patients with CF. The research team aims to validate the organoid screening model and to repurpose existing drugs for treating CF patients with rare mutations [5]. Apart from these academic aims they schedule periodical meetings with the clinicians to discuss the findings that may be of clinical relevance in the course of the Rainbow Project. During the periodical out-patient visit Jasper asks for the results on his organoids. Unfortunately, no response to existing drugs has been found during the Rainbow Project. Nevertheless, Jasper is hopeful that drugs will be found for him in the future. After all, his mini-guts remain stored in the biobank.

Simultaneously, the HUB distributes CF organoids nationally and internationally. The HUB is a so-called Living Biobank that aims to culture, collect, store, and distribute organoids from patients with various diseases including CF and cancer [6]. The HUB holds the intellectual property on organoid technology and distributes organoids to academic and commercial parties with objectives ranging from fundamental research to drug development. The CF organoids are for example used by academic parties to investigate disease mechanisms and gene-editing approaches. They are stripped from identifiers and transported to international companies (including overseas companies) to screen candidate drugs for CF.

References

1 Chakradhar S. Put to the test: Organoid-based testing becomes a clinical tool. *Nat Med* 2017;**23**:796–794.

2 Saini A. Cystic Fibrosis Patients Benefit from Mini Guts. *Cell Stem Cell* 2016;**19**:425–7.

3 Dekkers JF, Berkers G, Kruisselbrink E, *et al.* Characterizing responses to CFTR-modulating drugs using rectal organoids derived from subjects with cystic fibrosis. *Sci Transl Med* 2016;**8**:344ra84.

4 Boers SN, de Winter-de Groot KM, Noordhoek J, *et al.* Mini-guts in a dish: perspectives of

adult Cystic Fibrosis (CF) patients and parents of young CF patients on organoid technology. *J Cyst Fibros* 2018;**17**:407–15.

5 Van Mourik P, Berkers G, Vonk AM, *et al.* WS18.2 The rainbow project: personalised medicine for CF-patients with rare mutations. *J Cyst Fibros* 2017;**16S1**:S30.

6 Hubrecht Organoid Technology (HUB). http://hub4organoids.eu/ (accessed 25 September 2018).