Developing a patient-derived organoid biobank, suitable for large scale drug screenings

Poster #189

Lars-Eric Fielmich[1]*, Annemarie Buijs[1]*, Daniele Mori[1], Bas Viergever[2], Nihed Draoui[3], Anna Schepers[1], Mariana Silva[1], Eline van de Ven[1], Mathijs Scholtus[4], Tokameh Mahmoudi[4], Tahlita Zuiverloon[5], Jasper Mullenders[1], Merel Derksen[1], Paul Gavine[2], Sylvia F Boj[1], Richard Meijer[3], Onno Kranenburg[6], Janine Arts[2], Robert Vries[1]

*: equal contribution ; 1: HUB Organoids, The Netherlands ; 2: University Medical Center Utrecht - Urological Oncology Dpt., The Netherlands; 3: Janssen Biotech - Solid Tumors Targeted Therapies Dpt., Belgium; 4: Erasmus Medical Center Rotterdam – Biochemistry Dpt., The Netherlands; 5: Erasmus Medical Center Rotterdam – Urological Oncology Dpt., The Netherlands; 6: University Medical Center Utrecht - Translational Oncology Dpt., The Netherlands

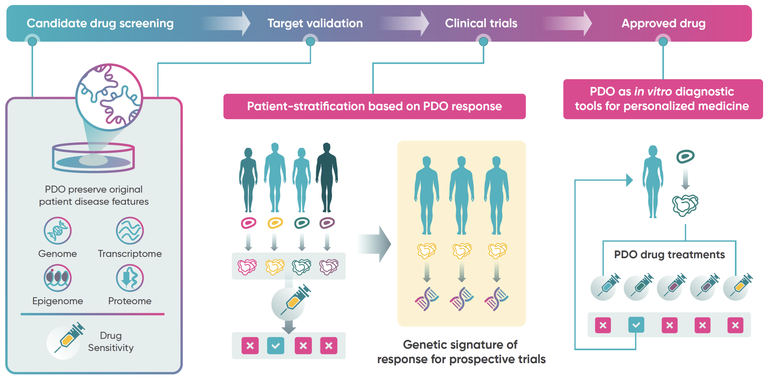
Janssen Research & Development, A Division of Janssen Pharmaceutica NV

Abstract

Conventional models for preclinical drug screening offer poor predictive value for patient response, causing high attrition rates of new agents in the clinic. HUB's proprietary Patient-Derived Organoid (PDO) Technology enables long-term expansion of primary patient material to generate 'mini organs in a dish' that can be used as patient avatars, thus bringing every "patient in the lab®".

Here we present the establishment of the first Non-Muscle-Invasive Bladder Cancer (NMIBC) PDO biobank comprising 50 PDO models from patient biopsies. Our biobank was extensively characterized at the clinical and molecular levels, confirming its value as highly representative of the NMIBC patient population. Next, we successfully identified potential new leads for further development by screening a panel of compounds for the treatment of bladder cancer on our PDO biobank.

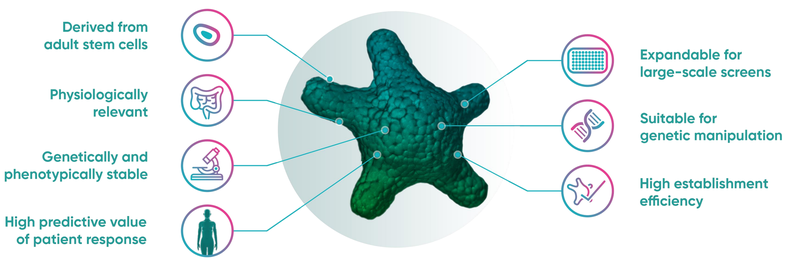
HUB Organoids® in drug development



HUB was founded to promote the commercialization of adult stem cell-derived organoid applications to predictive diagnostics, personalized medicine, clinical trials, regenerative medicine, and companion diagnostics. HUB Organoid Technology enables to culture *ex vivo* both diseased and normal tissue from most epithelia resulting in organoids that are stable in long-term culture, can be expanded and cryopreserved for multiple applications.

HUB Organoids are developed directly from patient material and preserve near-native tissue morphology and physiology, thus representing inter-patient and intra-tissue heterogeneity and bringing every patient in the lab.

HUB Organoids key features



Generating a patient-derived organoid biobank

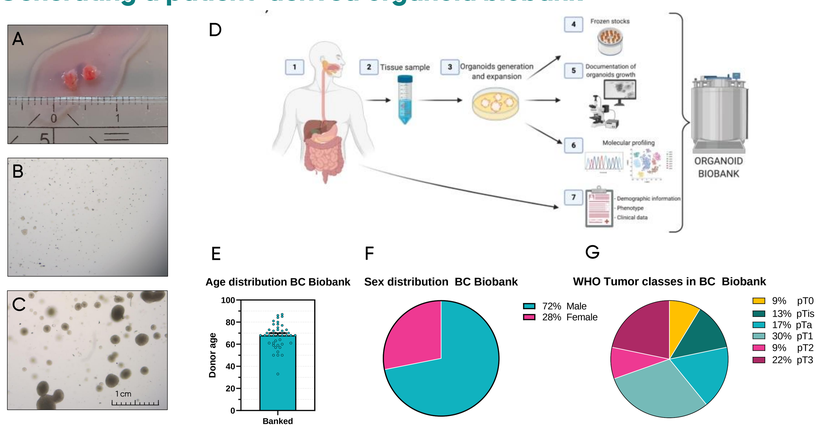


Figure 1. Generation of a NMIBC organoid biobank. Over the course of two years, biopsies were included from three medical centers. Patient material (A) was processed and plated (B), resulting in outgrowth of organoids in the first passage (C). After multiple rounds of expansion, an organoid model is validated and cryopreserved in the biobank (D). The resulting NMIBC biobank is representative of the patient population, as indicated by median age (E), sex ratio (F), and distribution of tumor stages (G). Biobanking success rate from eligible tissue was ~70%.

Clinical and molecular characterization of the biobank

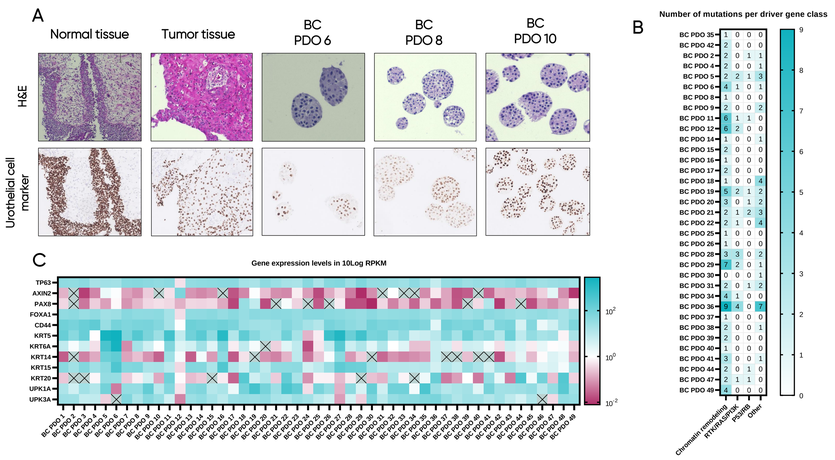


Figure 2. Characterization of NMIBC organoid biobank. (A) Histological analysis confirmed the bladder cancer origin of organoids derived from tissue (PDO 6 and 10) and urine (PDO 8) samples. The urothelium is organized and defined in normal tissue but disorganized in tumor tissue. (B) Summary of whole-exome DNAseq. Mutations in known bladder cancer driver genes were found in all BC organoid models in the biobank. (C) Summary of whole-transcriptome RNAseq. Analysis confirmed tissue identity of bladder cancer organoids. Additionally, expression of a known tumor initiating cell marker in bladder cancer was confirmed. *NB: characterization further includes pathology reports, patient history, and treatment follow-up, resulting in a well-annotated BC patient cohort in the lab.*

Candidate drug screen with viability readout of the biobank

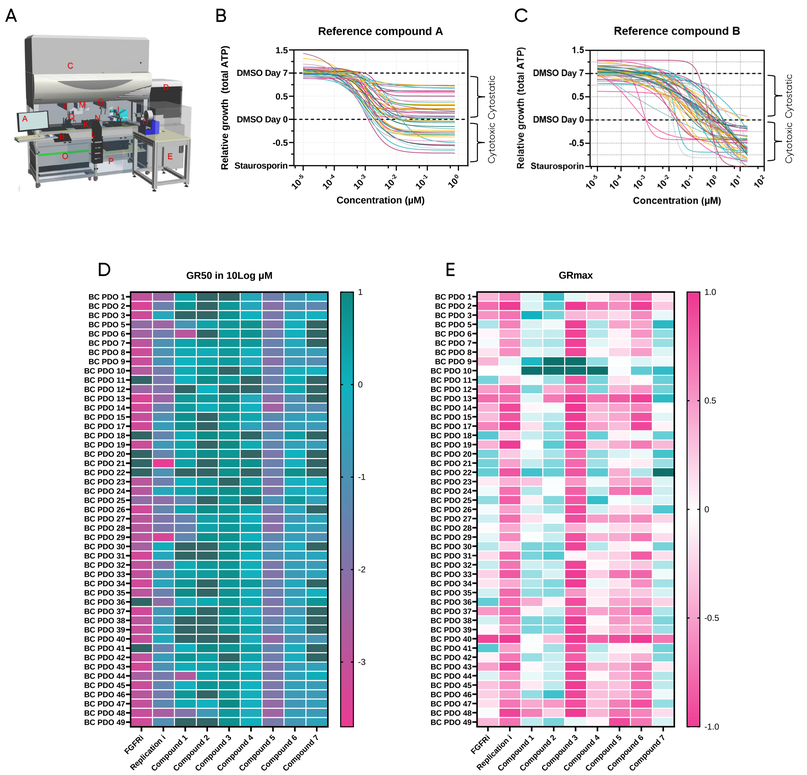


Figure 3. Compound screening of prospective drug leads. Dose-response of bladder cancer organoids to nine compounds was assessed by viability measurement (total ATP). (A) Automation of parts of the drug screening process. (B, C) Different organoid dose-response curves plotted as Growth Rate (GR) for Reference compound A (B) and Reference compound B (C). (D, E) Quantitative metrics from the dose response curve create an overview of the data collection. GR_{50} is the concentration at which 50% growth inhibition is achieved (in log_{10} µM). GR_{max} is viability at the highest concentration tested. Organoids respond similarly to Reference A in terms of GR_{50} (B and D), whereas much more variation is seen in the GR_{max} (B and E). Organoids respond differently to Reference B in terms of GR_{50} (C and D), whereas less variation is seen in the GR_{max}.

Conclusions

The work presented here shows the feasibility of

- Building PDO biobanks representative of a specific patient population
- Using PDOs in drug development to select next generation cancer drugs

Visit booth #2367 for more Information
Or contact us at: bd@huborganoids.nl

www.huborganoids.nl
Contact us