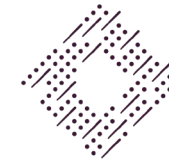


Organoid technology to accelerate therapeutic innovation



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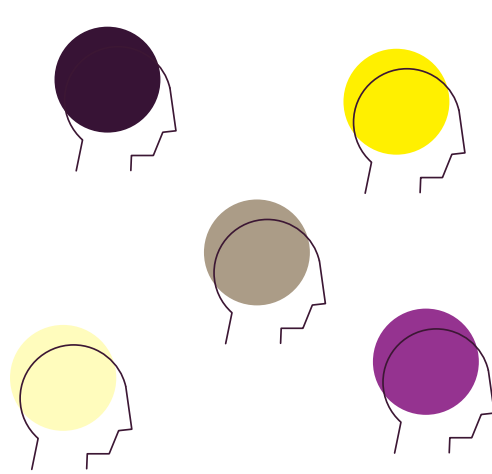
*Outsmarting cancer
Impacting lives*



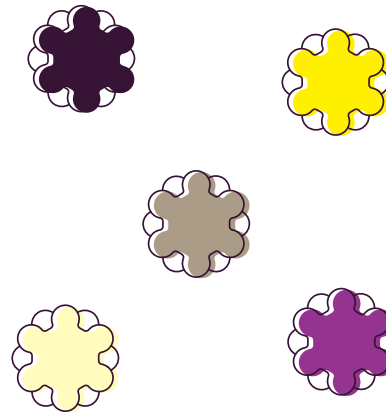
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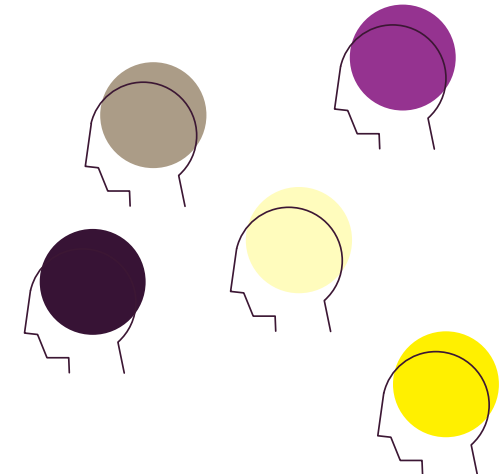
The problem: we need better preclinical cancer models



Heterogeneous
patient
population



Patient-specific
preclinical
models



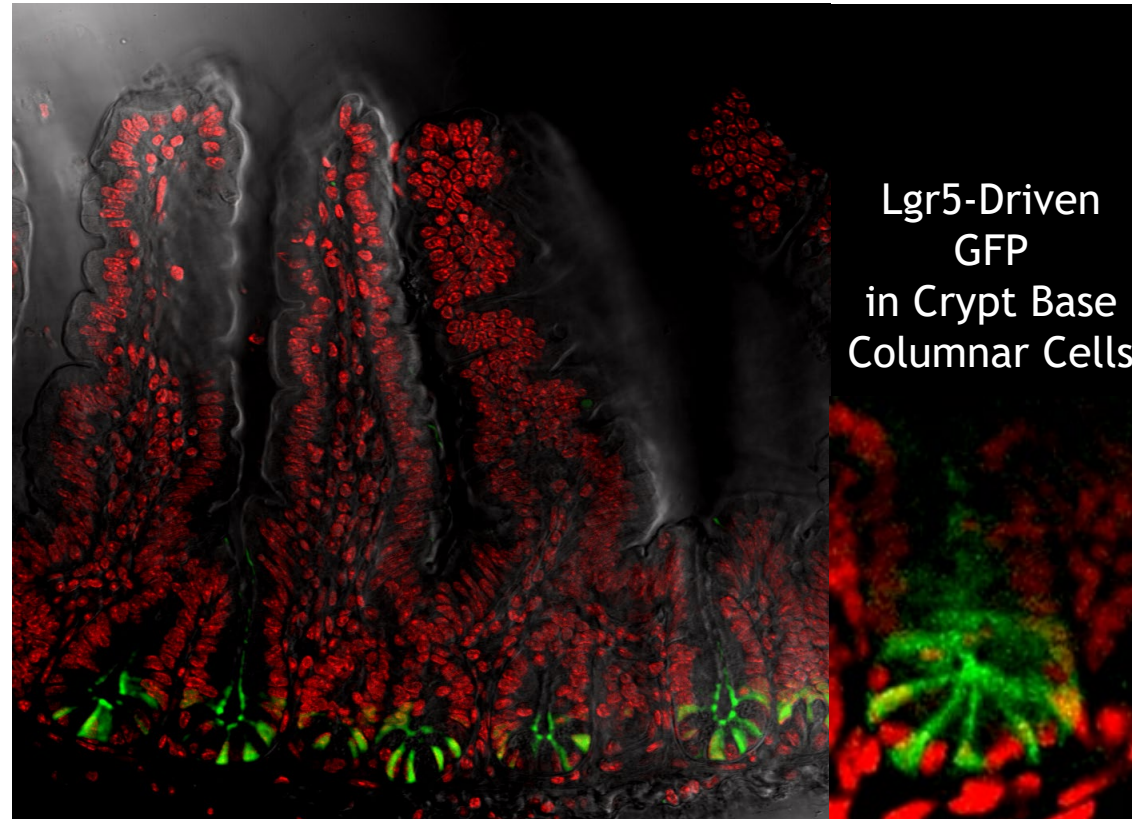
Heterogeneous
patient
population

Lack of preclinical models representative of patient tumors

- Patient **X**
- Cancer cell lines **X**
- Animal models **✓ / X**

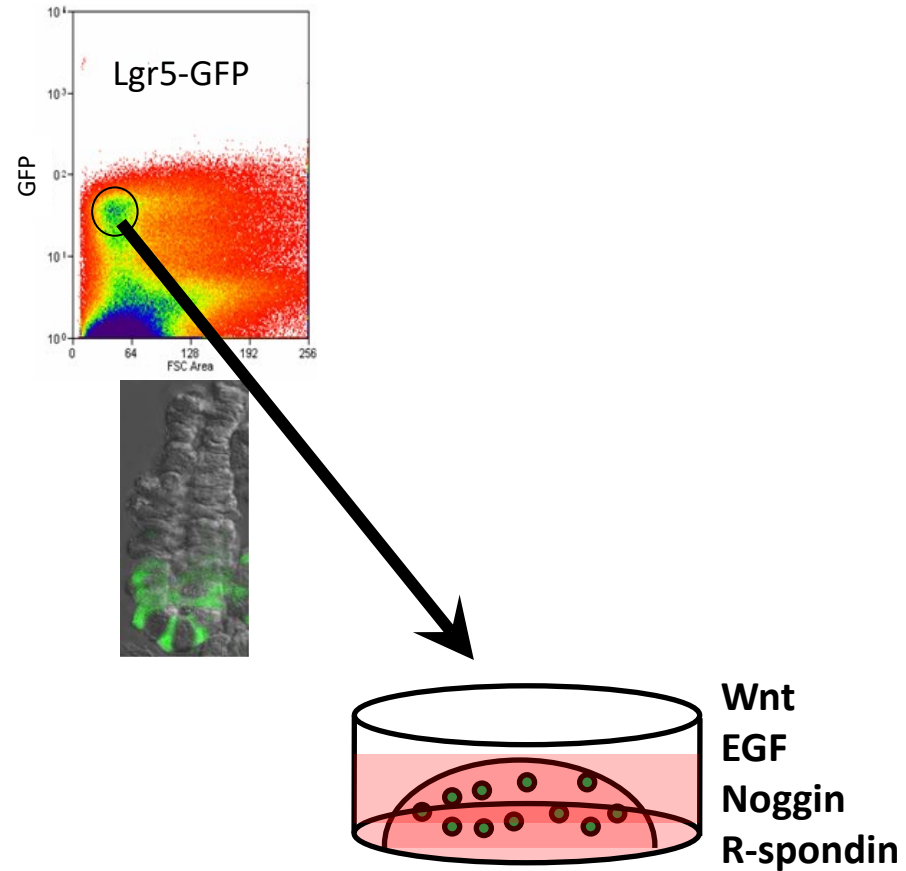
What is an organoid?

Lgr5 marks cycling stem cells in the intestine



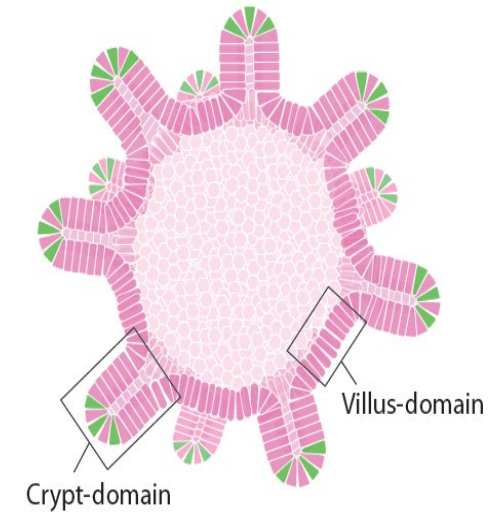
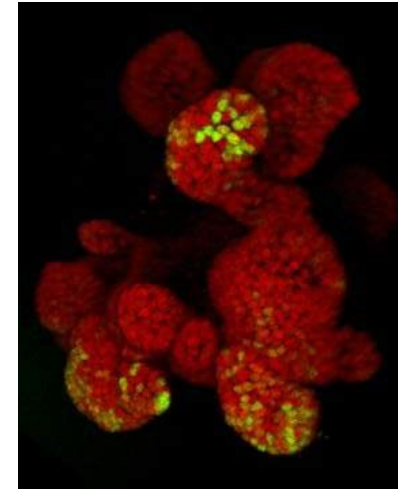
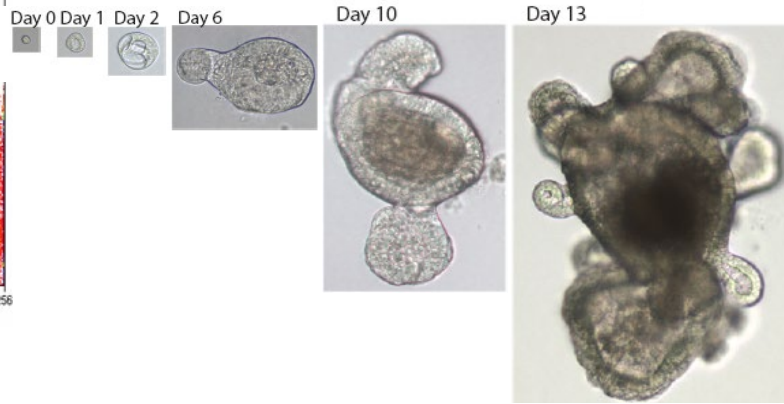
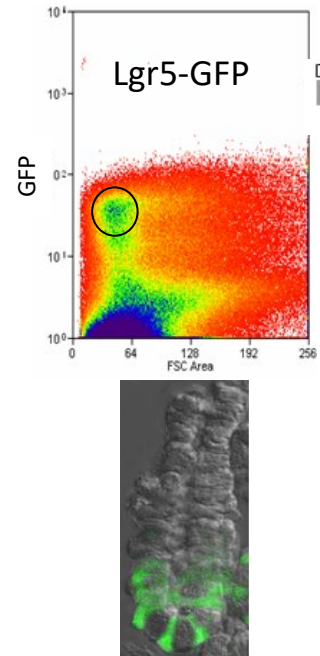
Barker et al, Nature 2007

Lgr5-positive intestinal stem cells can be expanded *in vitro* as “mini-guts”



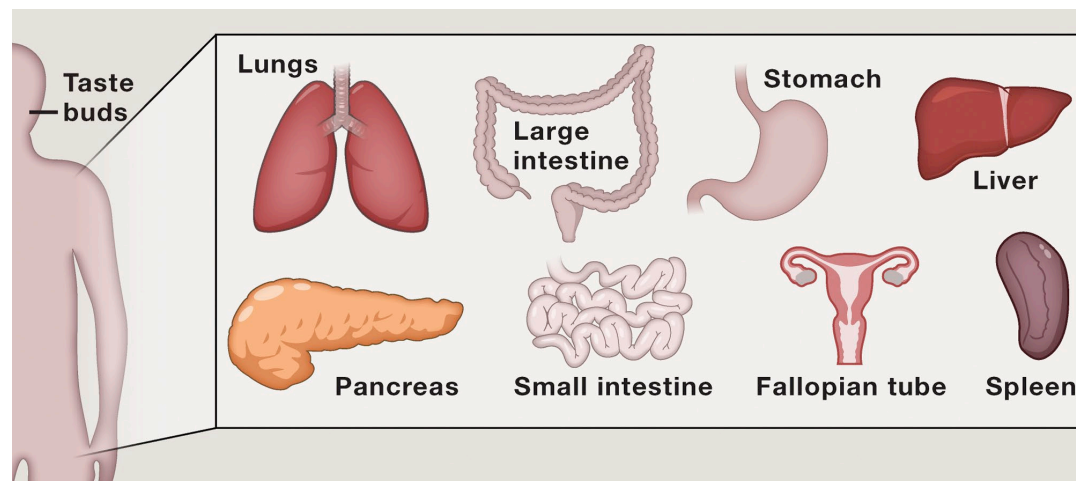
Sato et al, Nature 2009

Lgr5-positive intestinal stem cells can be expanded *in vitro* as “mini-guts”



Sato et al, Nature 2009

Organoids: stem cells in a dish



Clevers, Cell 2016

- Can be obtained with high efficiency from patient-derived tissue (healthy and diseased)
- Retain phenotypic and genetic features of native tissue
- Genetic modelling using gene editing

Drost et al., Nature 2015; Drost & van Boxtel et al., Science 2017; Drost & Clevers, Nat Rev Cancer 2018; Ganpat et al., under review (pre-print bioRxiv)

- Development of individualized therapies

- Adult cancer-derived organoids were shown to have predictive value for drug sensitivity

Vlachogiannis et al., Science 2018; Tiriác et al., Cancer Discov. 2018; Ooft et al., Sci Transl Med 2019; Ganesh et al., Nat Med 2019; Yao et al., Cell Stem Cell 2020



Organoiden Technologie: Personalized Medicine

Onco-Accelerator: Platform Organoids & Regulatory Innovation Workstream

- Shared PhD student (Puck Roos)
- Can organoids provide sufficient evidence for EMA approval of medicines?

Can organoid technology be applied to pediatric tumors?

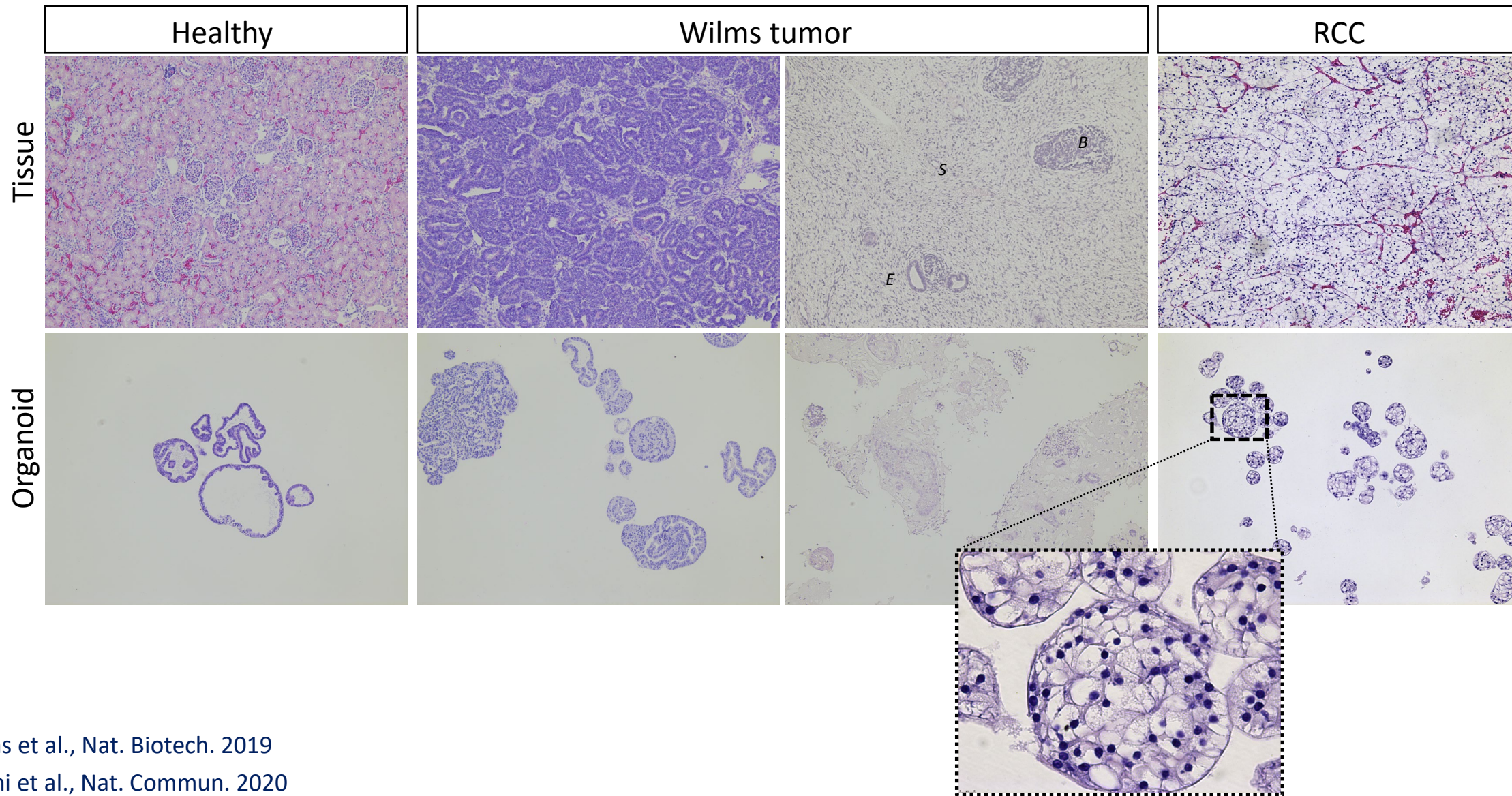
Pediatric versus adult malignancies

- Adult cancers > carcinomas; Pediatric cancers > heterogeneous (leukemias, lymphomas, brain and non-central nervous system tumors, sarcomas).
- Pediatric cancers > consequence of dysregulated development caused by a limited set of genetic alterations. Compared to adult cancers, pediatric cancers harbor fewer and different mutations.

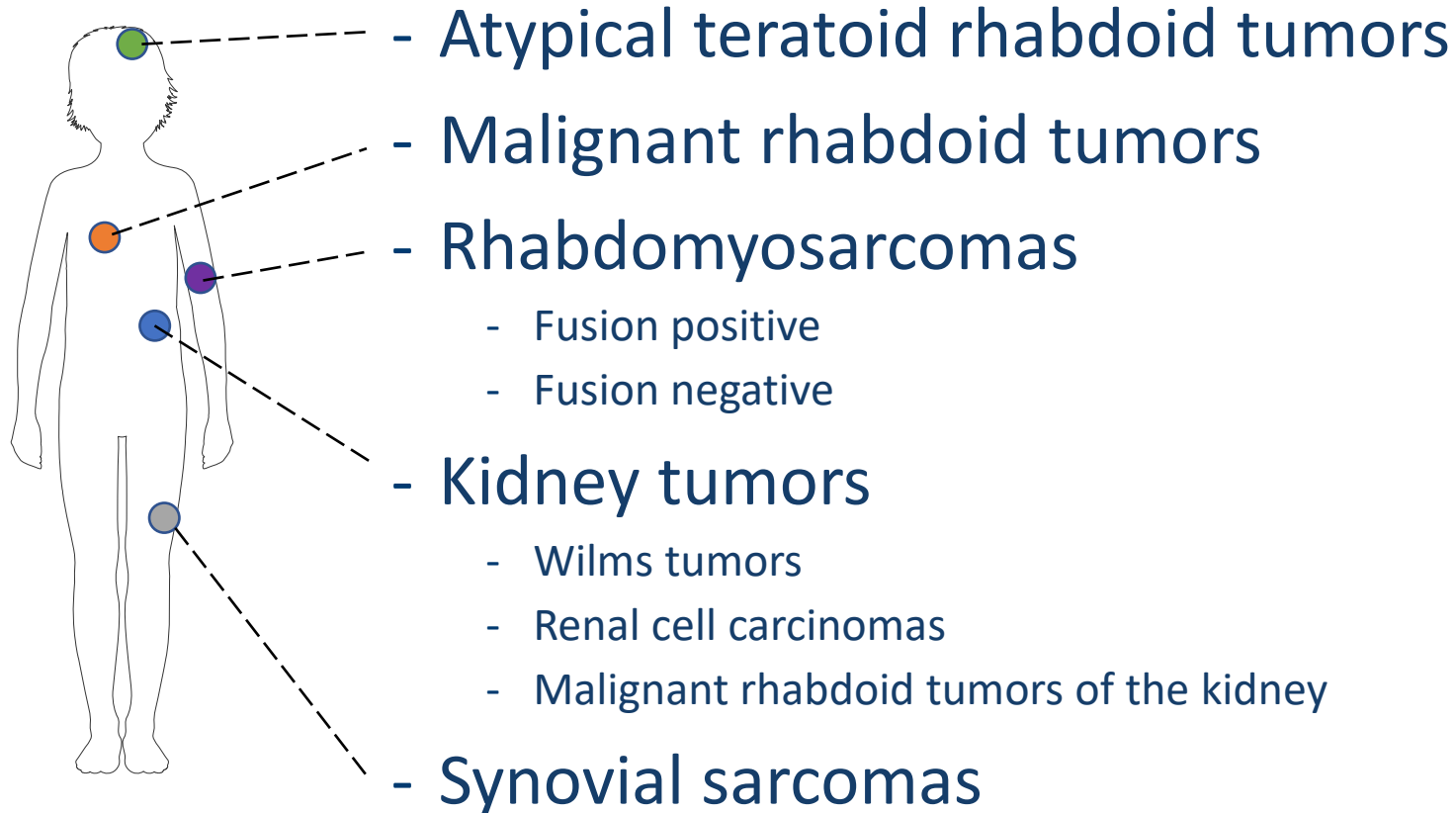
Culture conditions have to be optimized for every individual tumor entity:

- Growth factors
- Matrices

An organoid model for pediatric renal tumors



Drost group: Childhood solid tumor organoids

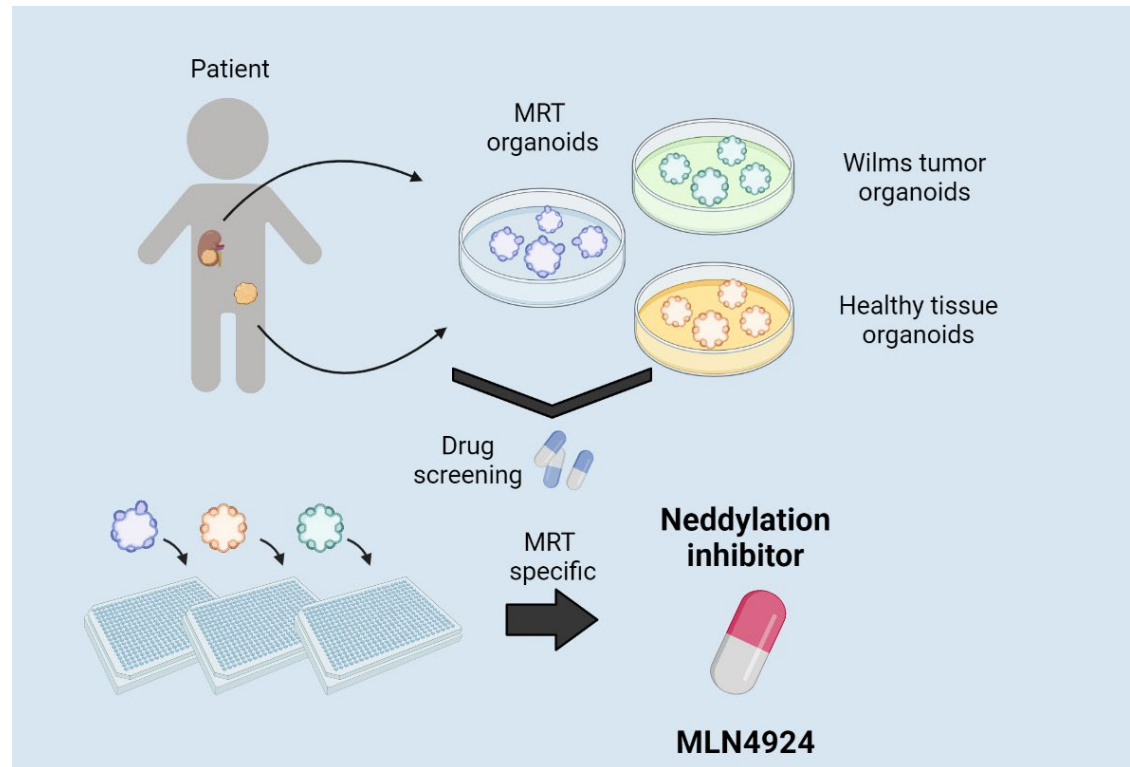


- Whole genome sequencing
- RNA sequencing
- DNA methylation profiling
- Histology

Summary

- Pediatric cancer organoids are representative of patient tumors.
- Can be used to, amongst others:
 - study the molecular processes underpinning tumorigenesis in a **patient specific manner**
Custers et al., Nat. Commun. 2021; Liu et al., Nat. Commun. 2023
 - do low-/medium/high-throughput drug screen to find drug vulnerabilities
Calandrini et al., Cell Rep. 2021; Calandrini et al., STAR Protoc. 2022

As drug screen platform



Calandrini et al., Cell Rep. 2021
Calandrini & Drost, STAR Protoc. 2022

Summary

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- Can be used to, amongst others:
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 - do low-/medium/high-throughput drug screen to find drug vulnerabilities
Calandrini et al., Cell Rep. 2021; Calandrini et al., STAR Protoc. 2022
 - find tumor-specific metabolic vulnerabilities
Kes et al., under review
 - establish co-cultures with normal cells, such as immune cells to develop immunotherapies
DeMunter, Buhl et al., under review; Barisa et al., under review, Buhl et al., in preparation.

Acknowledgements

Princess Máxima Center Group Drost

Jeff De Martino
Juliane Buhl
Irene Paassen
Yvonne Tiersma
Sofia Doulkeridou
Charlotte op 't Hoog
Rugile Januskeviciute
Michael Meister
Maroussia Ganpat
Nhung Pham
Jiayou He
Marjolein Kes
Puck Veen

Terezinha de Souza
Marian Groot-Koerkamp
Carla Rios Arceo
Kim Schellekens
Mariel Brok
Giulia Peticari
Nadia Anderson
Helena Viñas Gaza
Emma van Amersfoort
Katie Nachataya
Mark Dings

Dept. Neuro-oncology
Eelco Hoving, Niels Franken

Dept. Solid tumors
Marry van den Heuvel-Eibrink,
Ronald de Krijger, Alissa Groenendijk

Single Cell Genomics Facility
Thanasis Margaritis
Aleksandra Balwierz
Tito Candelli
Philip Lijnzaad
Lindy Visser
Wim de Jonge

The Netherlands Cancer Institute
Elzo de Wit

Erasmus Medical Center
Ningqing Liu

KiTZ, DKFZ, Heidelberg (Germany)
Marcel Kool

Sanger Institute, Hinxton (UK)
Sam Behjati

St. Jude Children's Research Hospital,
Memphis (US)
Martine Roussel

Andrew Davidoff, Andrew Murphy



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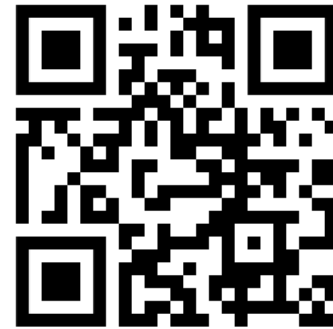
Outsmarting cancer
Impacting lives





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D R O S T

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