University of Antwerp
CORE | Center for Oncological Research

Colorectal Cancer and Organoids

BSCRS 21st Post-Graduate Course

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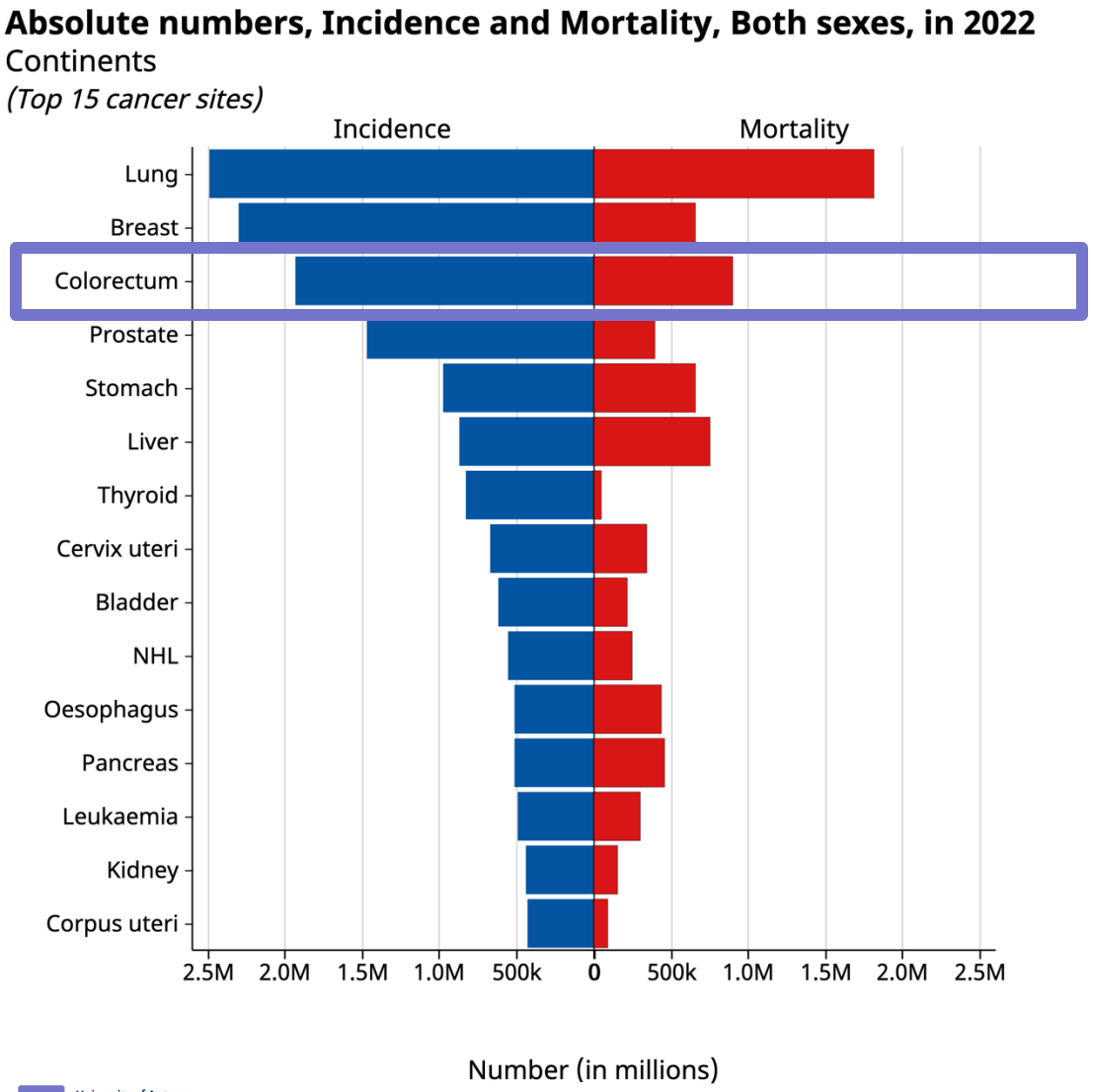
Background on CRC



- **Challenges:**
  - Late diagnosis
  - Tumor heterogeneity (inter & intra)
  - Drug resistance

- **Need for <u>better models</u> to predict therapeutic efficacy and study CRC biology.**

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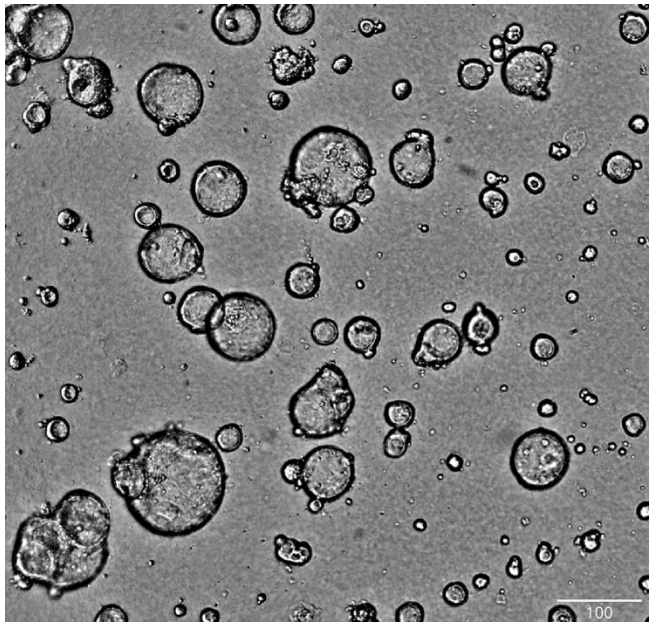
Cancer TODAY | IARC - https://gco.iarc.who.int/today
Data version : Globocan 2022 (version 1.1)

What are organoids?

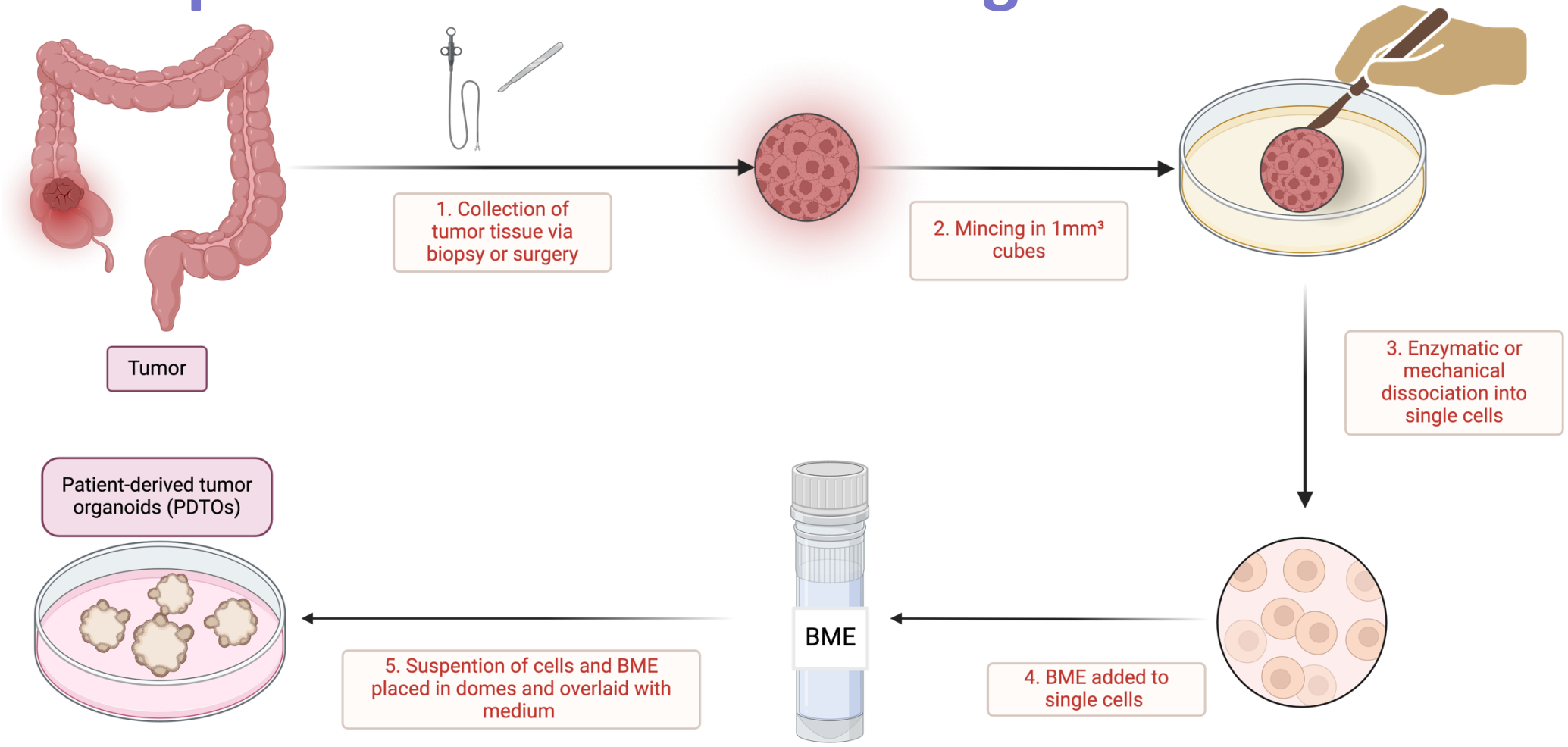
- **3D cell cultures**

- derived from **stem cells**
  - Adult stem cell (*= patient-derived)*
  - Induced pluripotent stem cells (iPSC)



- replicate tissue **architecture, function and behaviour**

How are patient-derived tumor organoids made?

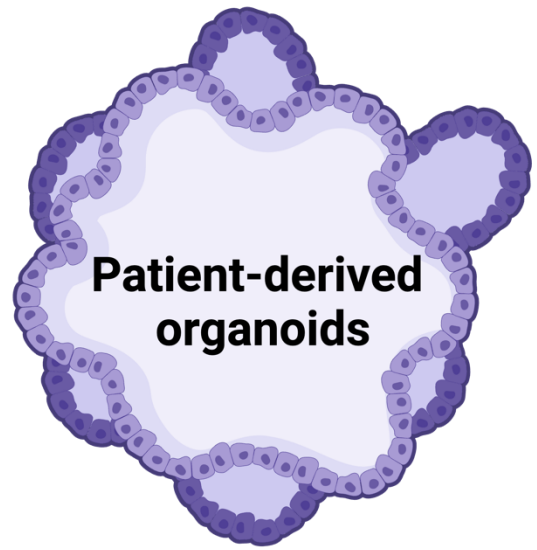


BME = basement membrane extract

van der Graaff, D.; Seghers, S.; Vanclooster, P.; Deben, C.; Vandamme, T.; Prenen, H. Advancements in Research and Treatment Applications of Patient-Derived Tumor Organoids in Colorectal Cancer. *Cancers* **2024**, *16*, 2671. https://doi.org/10.3390/cancers16152671

Advantages

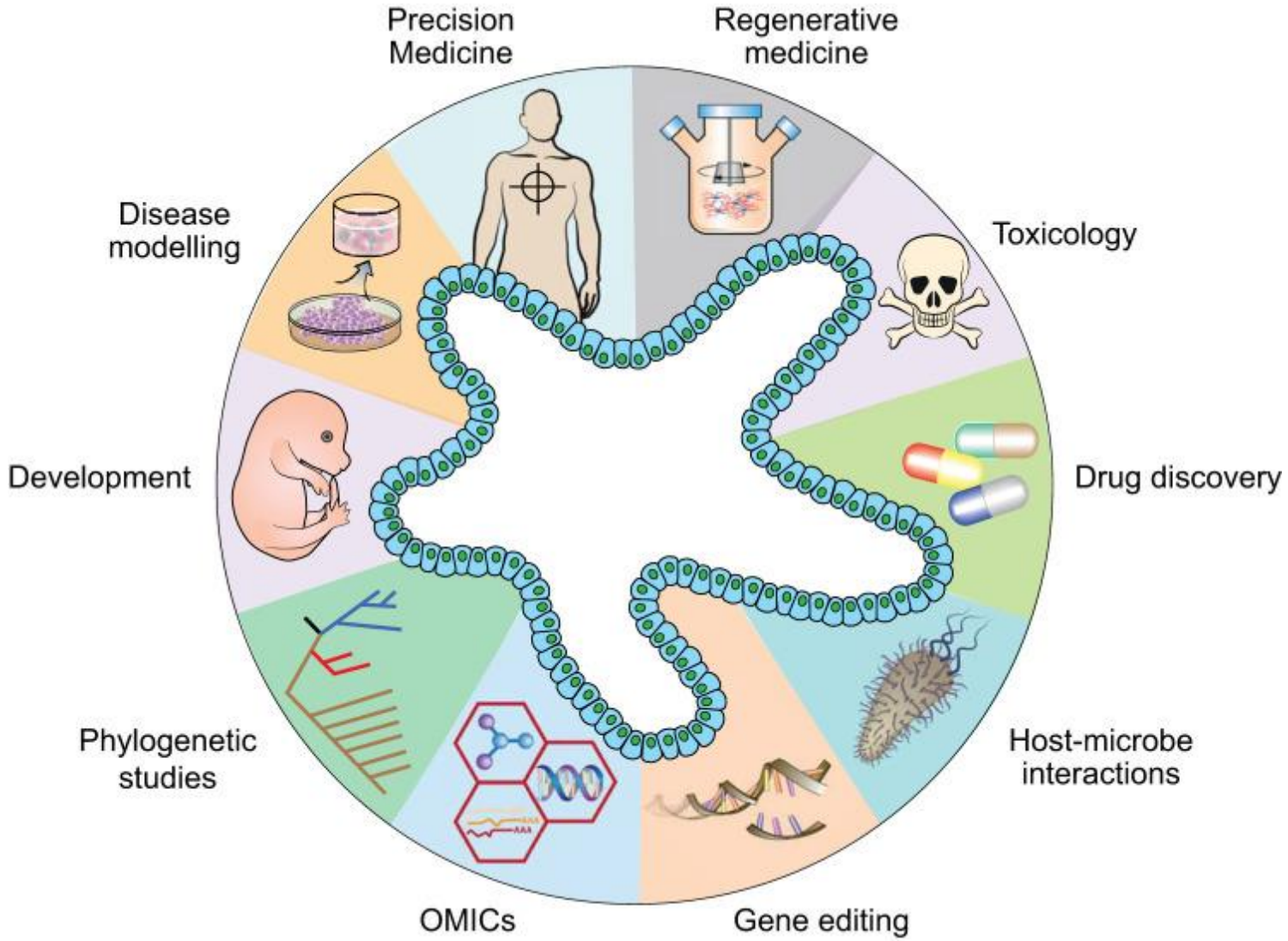
- Physiological relevance
  - Architecture
  - Function
- 3D culture
- Genetic stability
- Patient-specific
- High-throughput
- Disease modeling
- Long-term storage & culture
- Genetic manipulation
- Ethical advantage



Disadvantages

- Cost
- Complexity
- Variability
- Standardization
- Time-consuming
- Limited scalability
- Limited lineage diversity
- Technical skill
- Data interpretation

Image made with biorender



Corrò C, Novellasdemunt L, Li VSW. A brief history of organoids. Am J Physiol Cell Physiol. 2020 Jul 1;319(1):C151-C165. doi: 10.1152/ajpcell.00120.2020.

Organoids in CRC research

Tumor biology

- Heterogeneity
- Evolution
- Tumor microenvironment
- …

Genetic study

- CRISPR/Cas9

Drug screening

- Drug repurposing
- Novel dugs
- Novel combination strategies
- Therapeutic vulnerabilities
- Biomarker discovery
- …

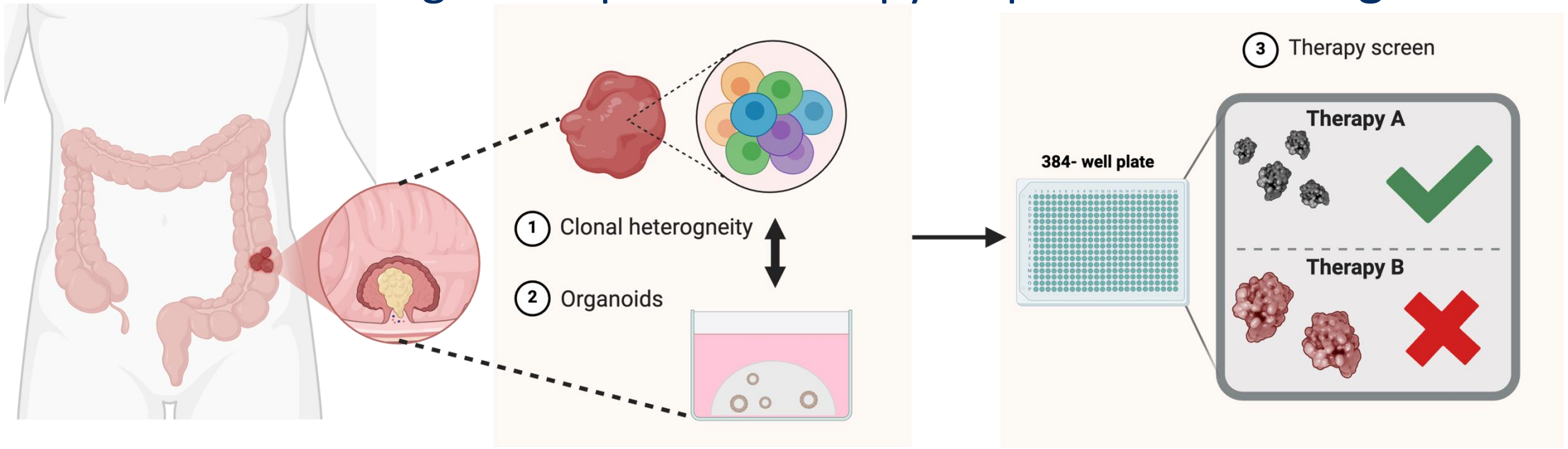
Many more

- …

For overview: van der Graaff, D.; Seghers, S.; Vanclooster, P.; Deben, C.; Vandamme, T.; Prenen, H. Advancements in Research and Treatment Applications of Patient-Derived Tumor Organoids in Colorectal Cancer. *Cancers* **2024**, *16*, 2671. https://doi.org/10.3390/cancers16152671

Personalized medicine and organoids

- Patient-derived organoids predict therapy response – “**chemogram**”



- Integration with omics (genomics, transcriptomics) for precision oncology.

Research highlights from our university

Biobanking & characterisation

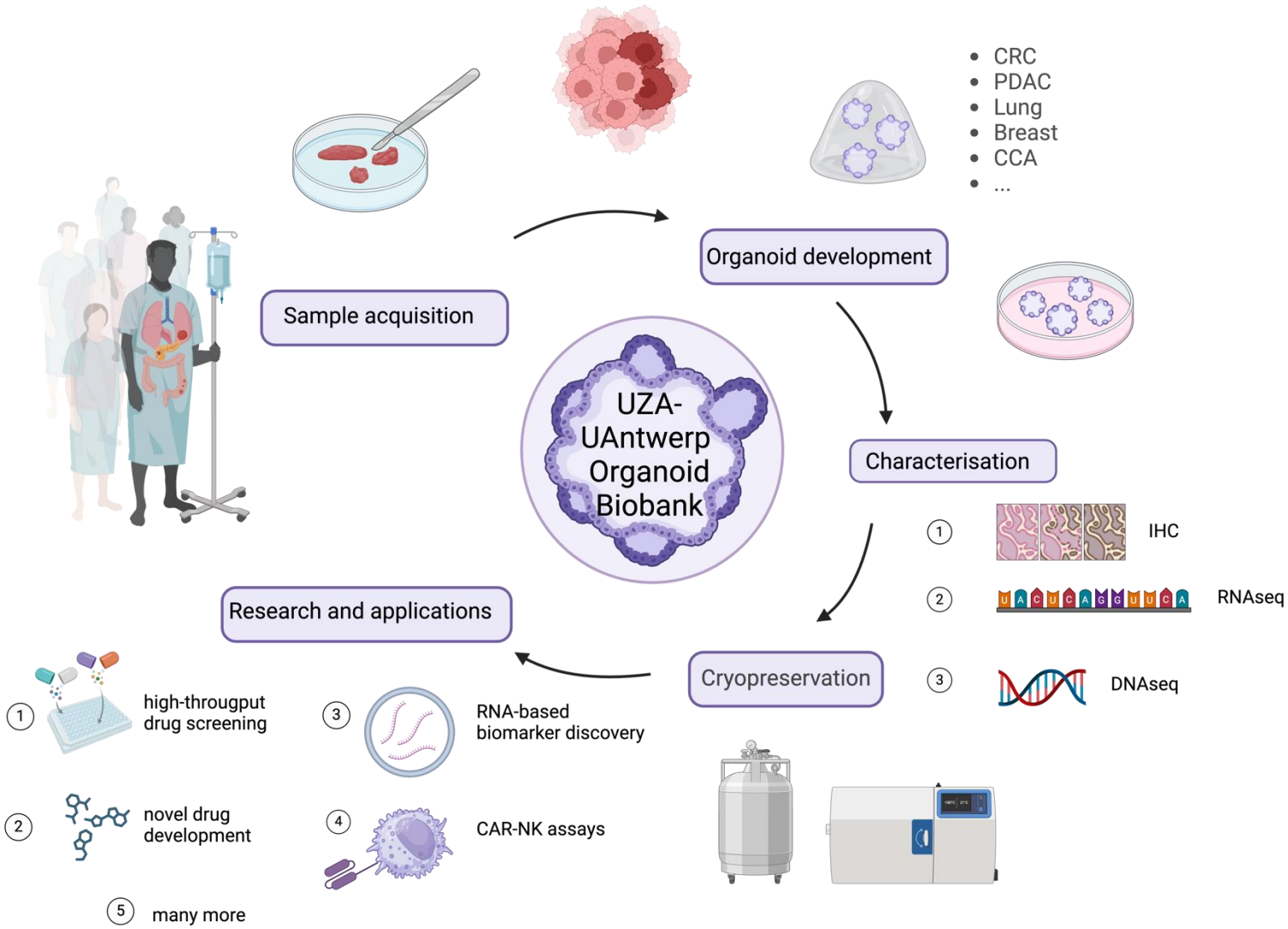


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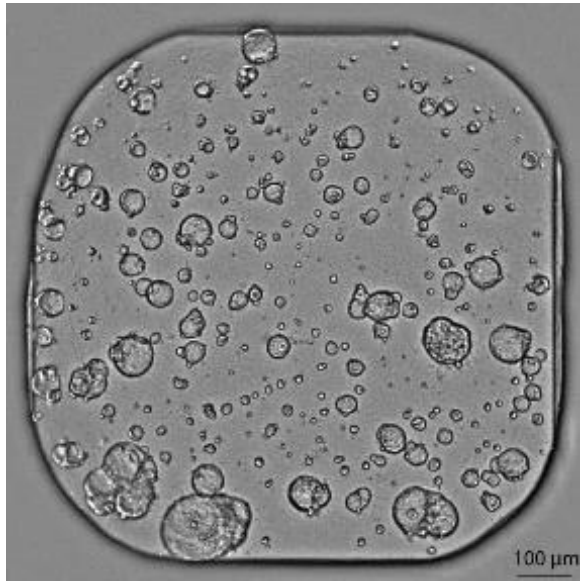
Figure made with biorender[10]

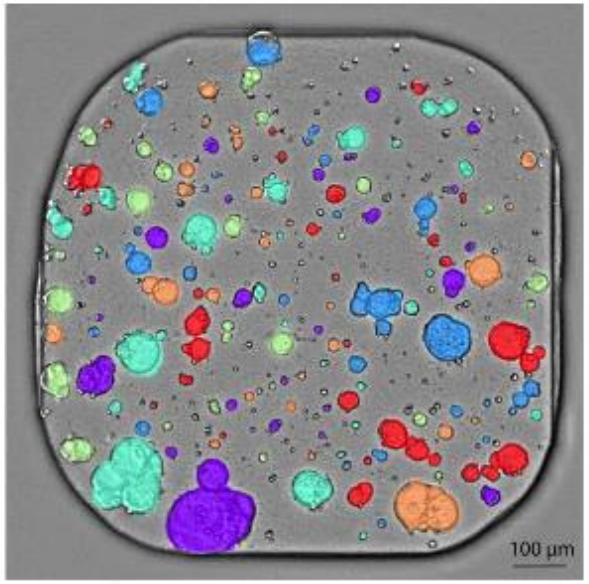
Abbreviations: CAR-NK, Chimeric antigen receptor-natural killer cell therapy, CCA, cholangiocarcinoma CRC, colorectal cancer; IHC, immunohistochemistry; PDAC, pancreatic ductal adenocarcinoma

Response prediction

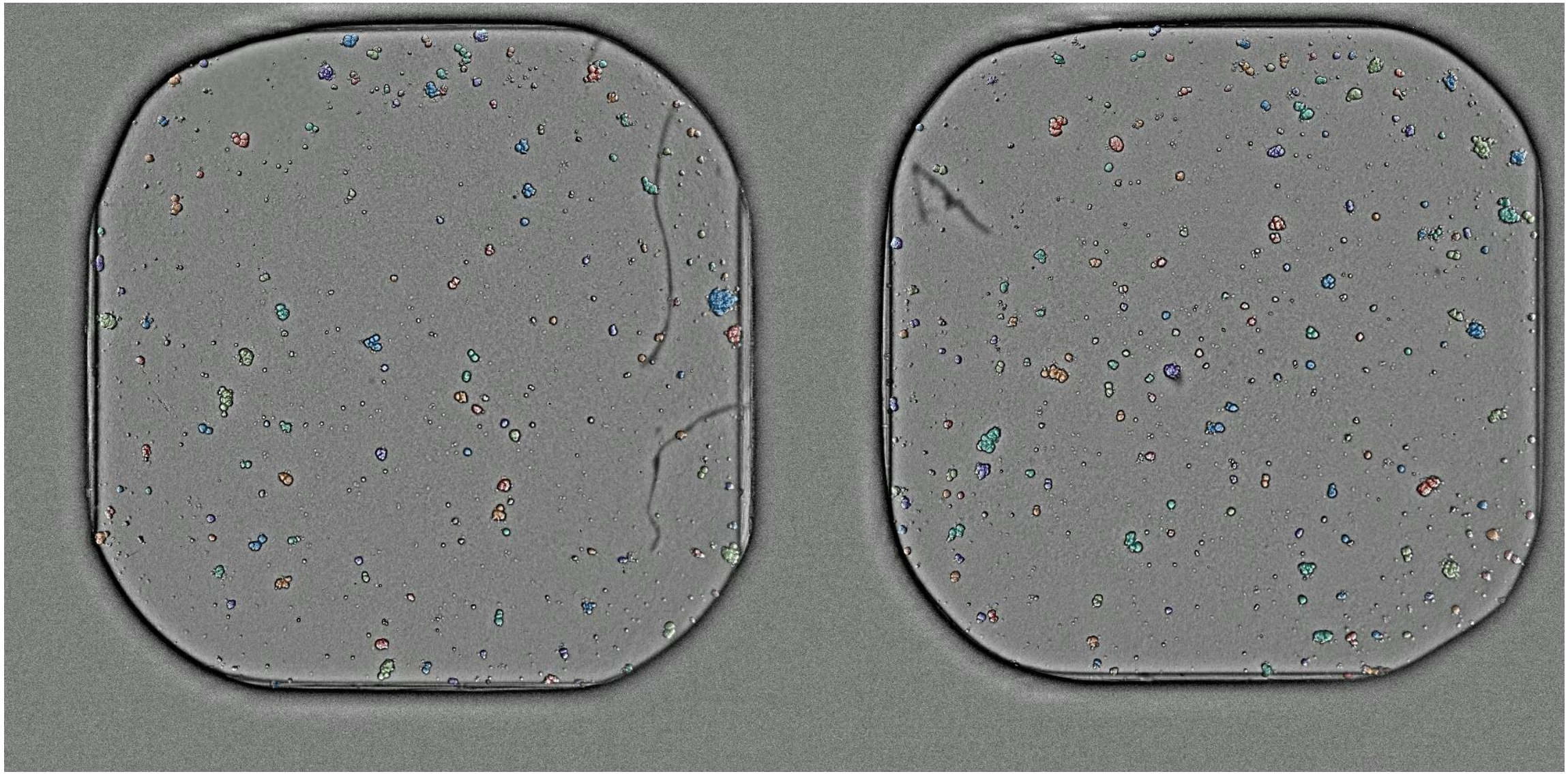
Orbits

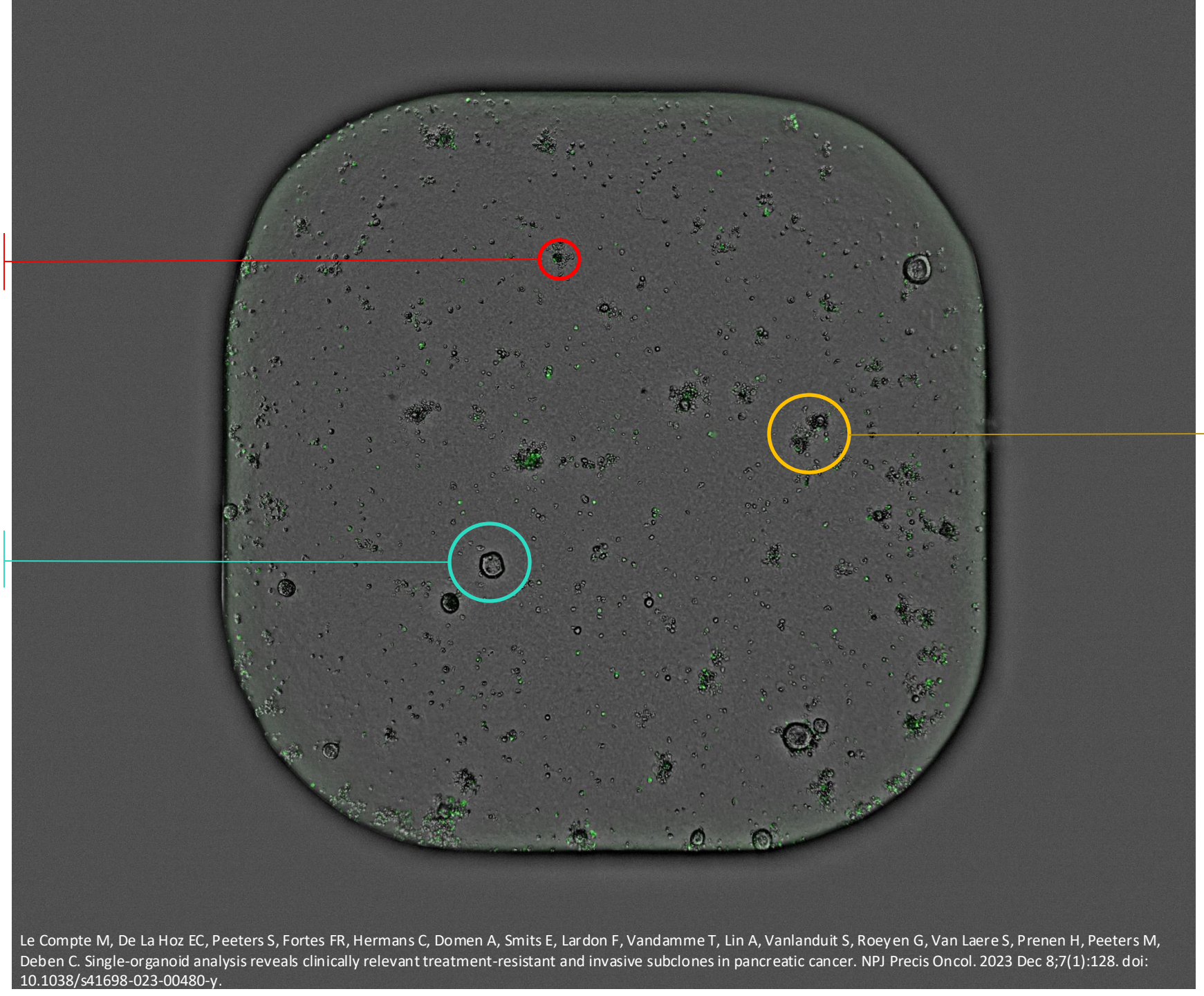
- Single organoid & whole-well read-out
- Viability and growth rate
- Migration and invasion
- Kinetic and endpoint
- Cytostatic vs cytotoxic drug response
- Sub-clonal response dynamics
- Next-gen drug metrics (NDR/NOGR)
- More..





Deben C, De La Hoz EC, Compte ML, Van Schil P, Hendriks JMH, Lauwers P, Yogeswaran SK, Lardon F, Pauwels P, Van Laere S, Bogaerts A, Smits E, Vanlanduit S, Lin A. OrBITS: label-free and time-lapse monitoring of patient derived organoids for advanced drug screening. Cell Oncol (Dordr). 2023 Apr;46(2):299-314. doi: 10.1007/s13402-022-00750-0.





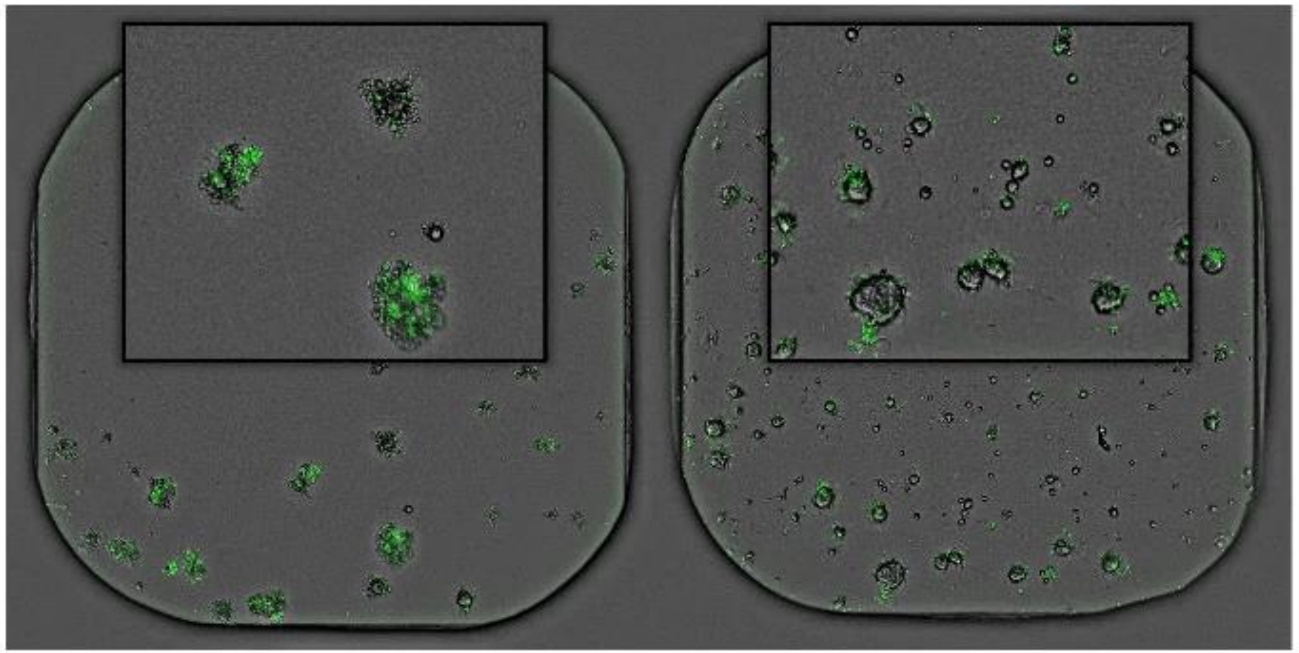
Le Compte M, De La Hoz EC, Peeters S, Fortes FR, Hermans C, Domen A, Smits E, Lardon F, Vandamme T, Lin A, Vanlanduit S, Roeyen G, Van Laere S, Prenen H, Peeters M, Deben C. Single-organoid analysis reveals clinically relevant treatment-resistant and invasive subclones in pancreatic cancer. NPJ Precis Oncol. 2023 Dec 8;7(1):128. doi: 10.1038/s41698-023-00480-y.

Personalised medicine

Prediction of progression or relaps

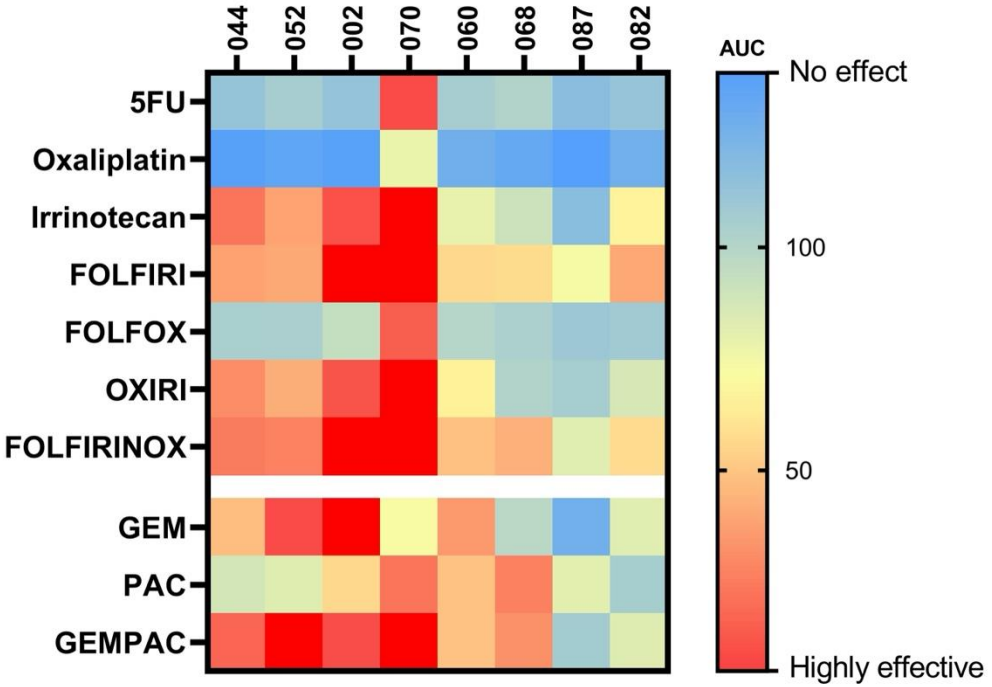
Time to relapse: **50 months**

Time to relapse: **6 months**



Patient 1

Patient 2

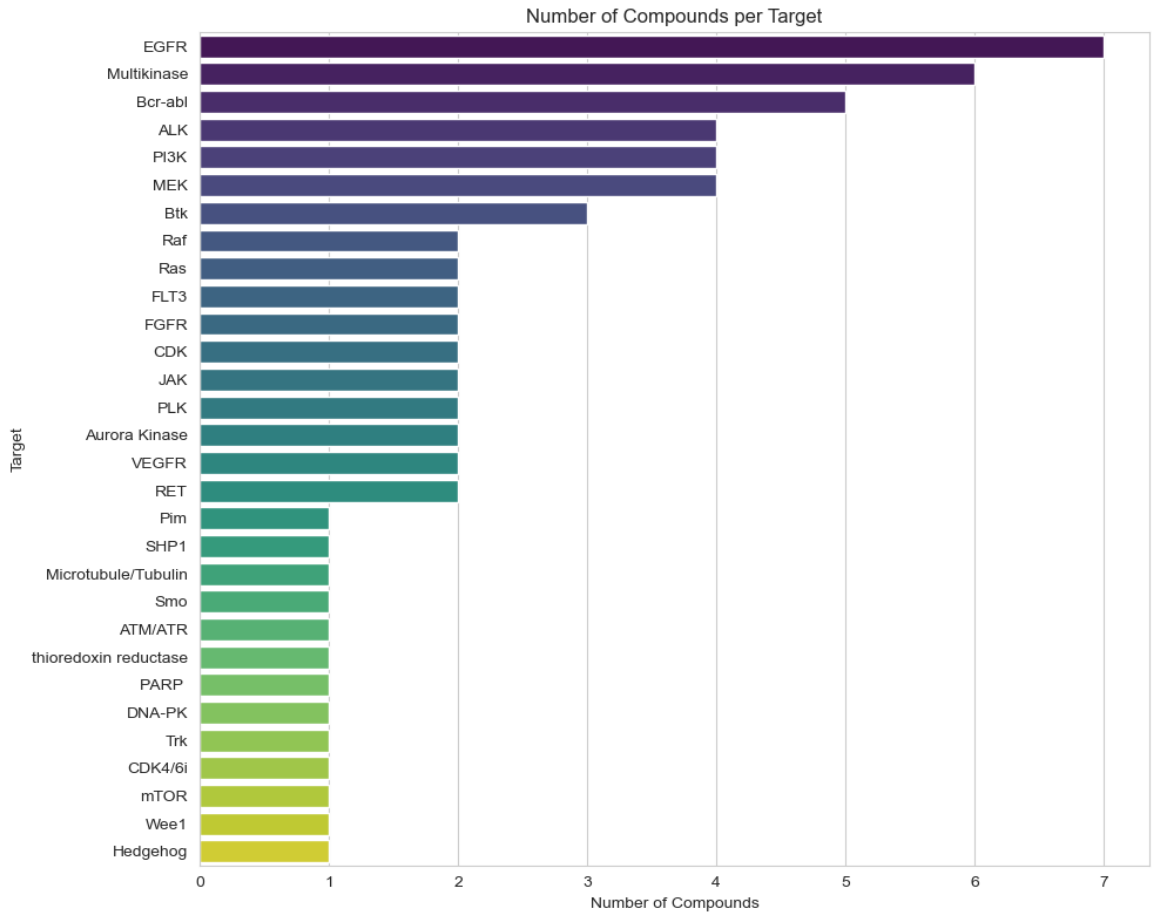


Research highlights from our university

- **Specific research topics**
  - 5FU potentiator → high trougput drug screening
  - Malignant effusions → novel sources for organoid generation
  - CAR-NK → combination strategies with cell therapy
  - SIGHTERA →AI-based drug discovery with organoid data
  - …

High througput drug screening

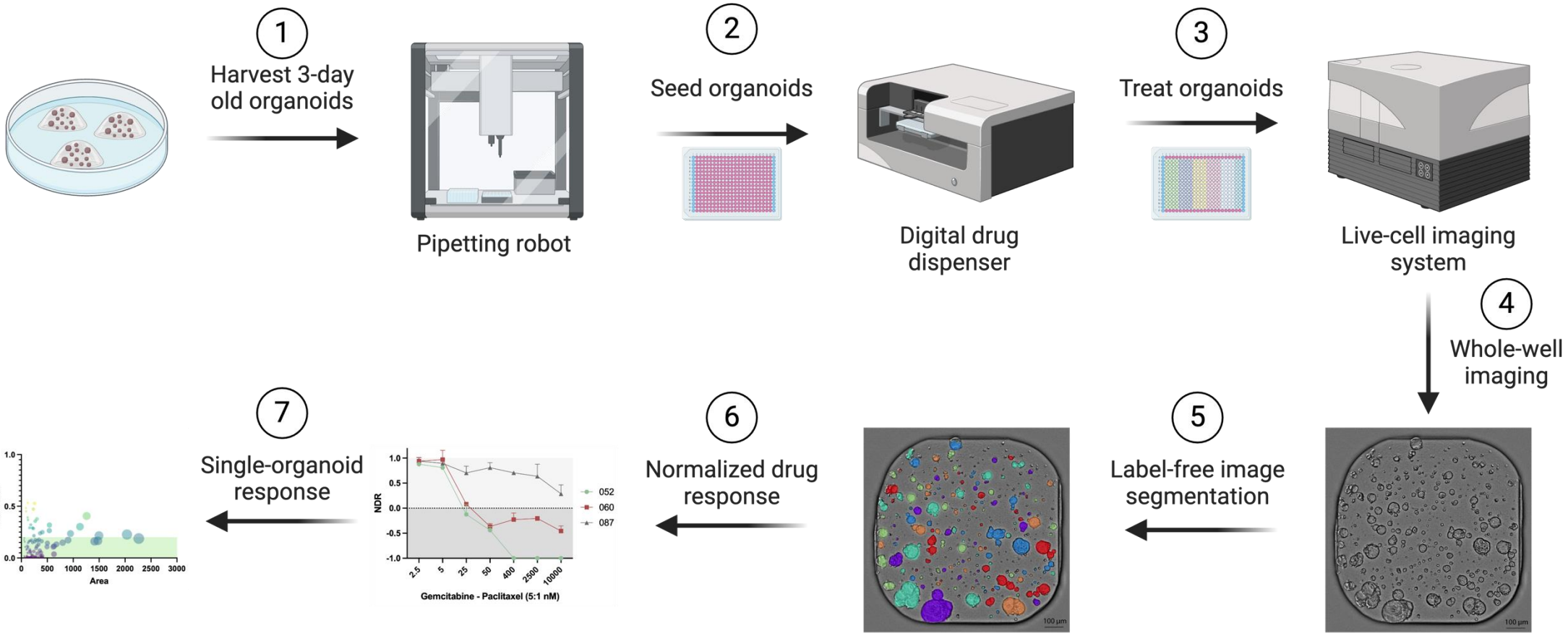
- 5FU potentiator



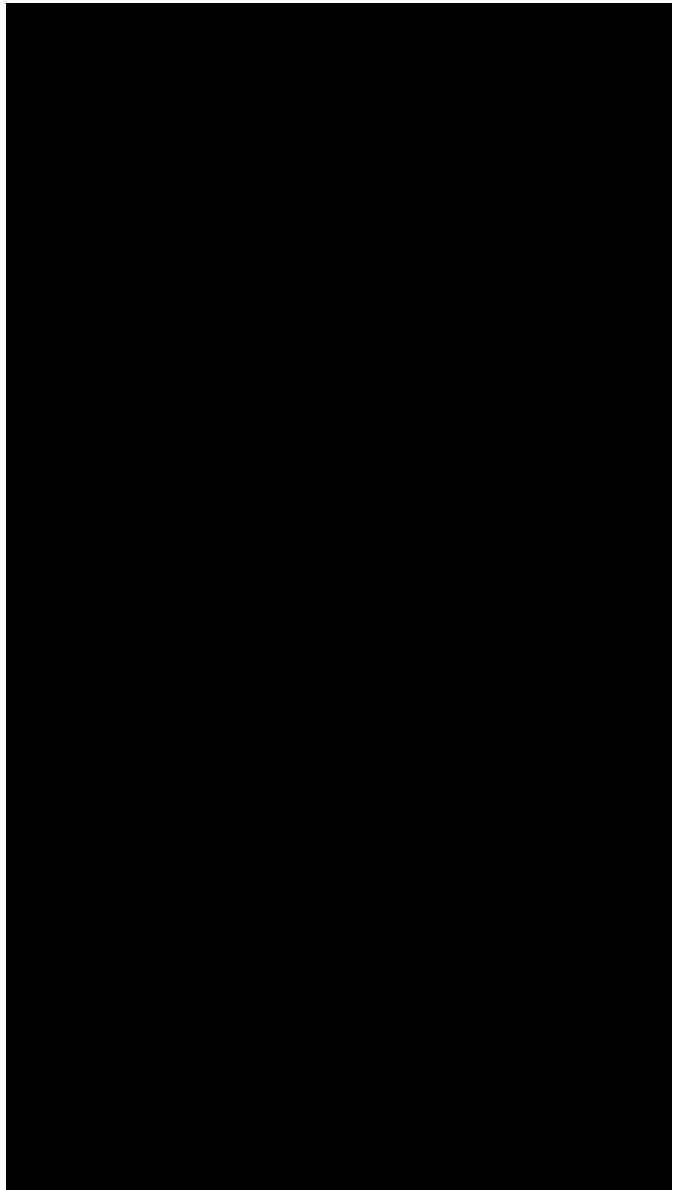
n = 98

High througput (HT) drug screening

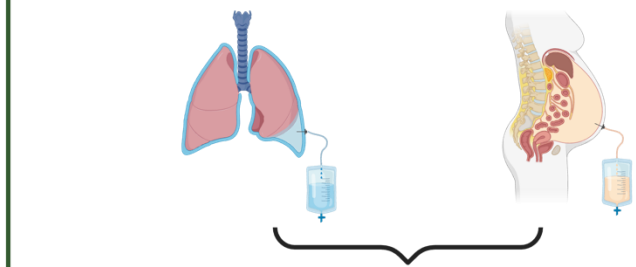
- 5FU potentiator



High througput drug screening



Malignant effusions



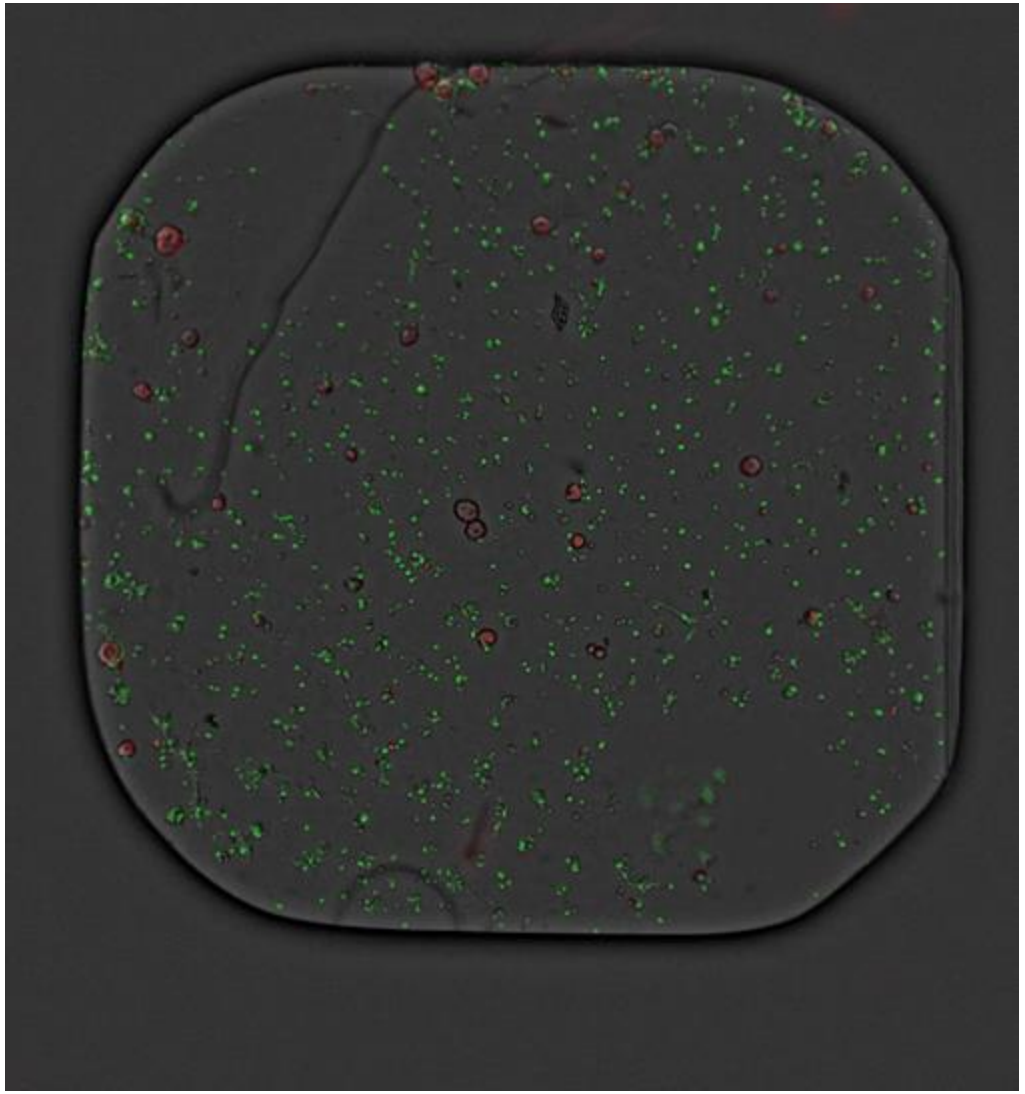
Robuste source for organoid generation

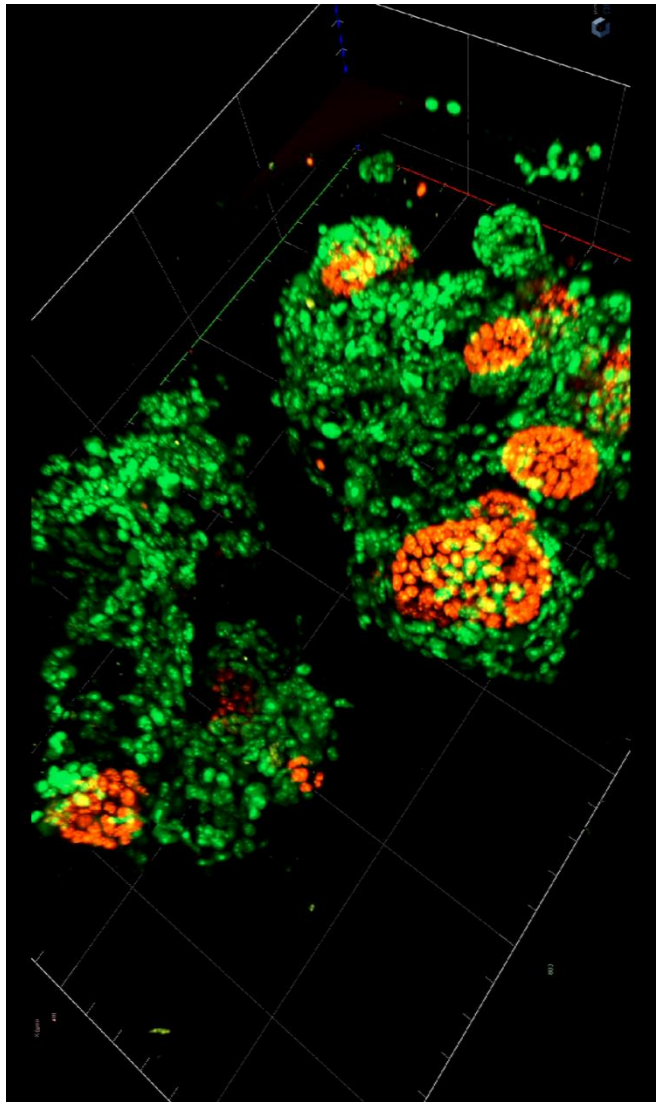
- Less invasive
- Less expensive
- Sequential organoid generation
- Higher success rates
- High purity
- Advanced tumors

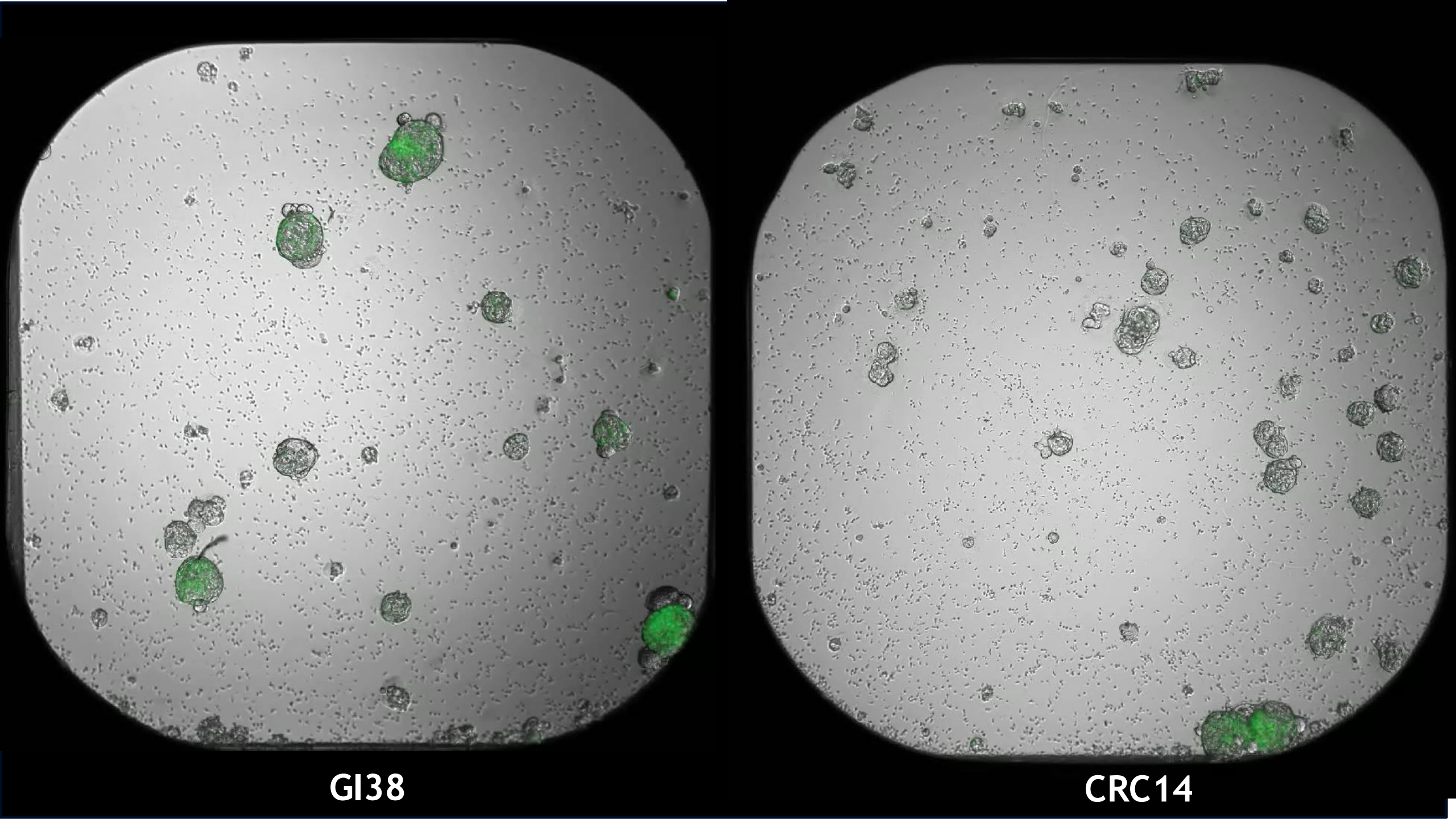
- Only in metastatic setting
- Some samples have low cellularity
- Absence of tumor micro environment

Seghers S, Le Compte M, Hendriks JMH, Van Schil P, Janssens A, Wener R, Komen N, Prenen H, Deben C. A systematic review of patient-derived tumor organoids generation from malignant effusions. Crit Rev Oncol Hematol. 2024 Mar;195:104285. doi: 10.1016/j.critrevonc.2024.104285

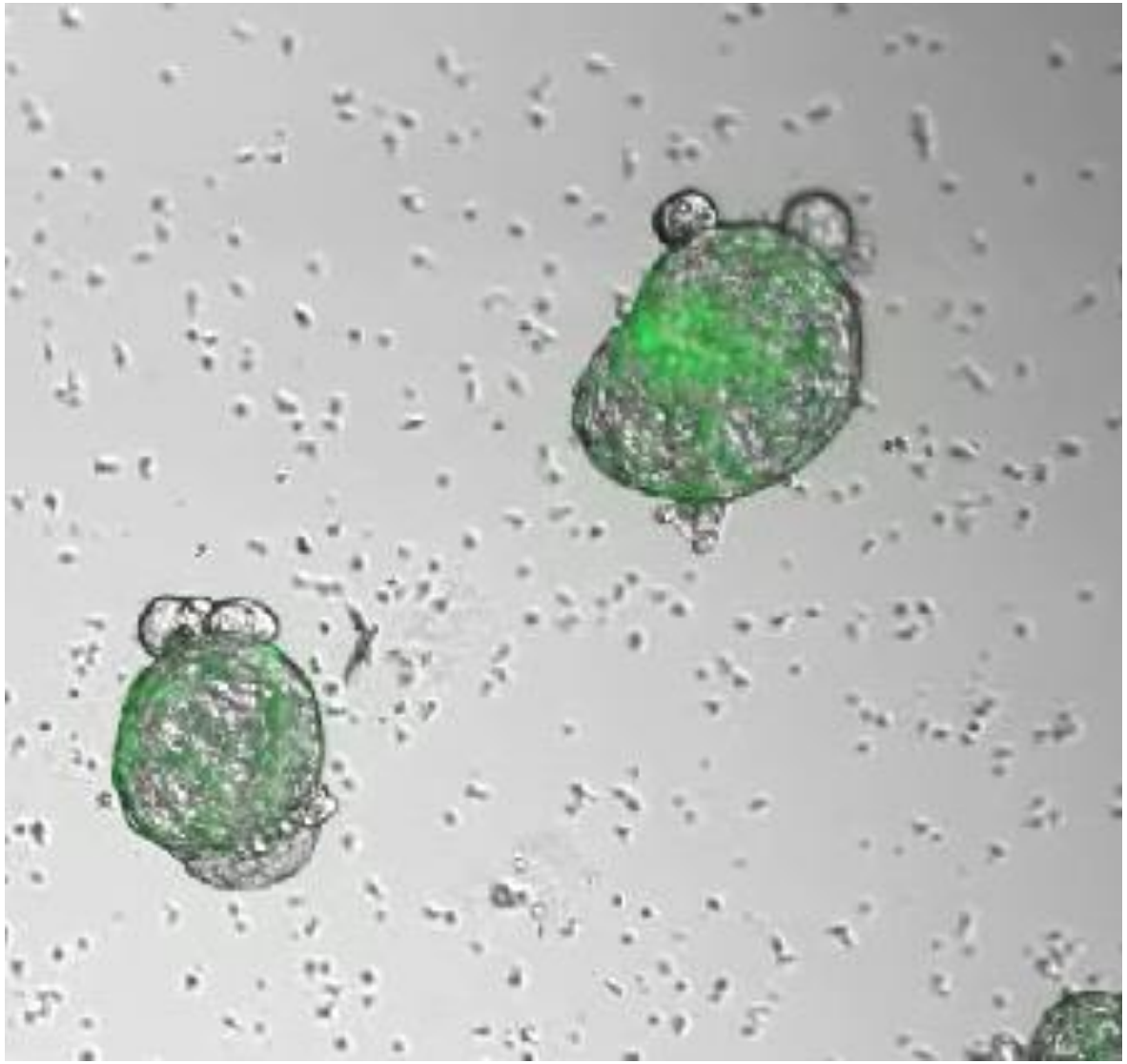
CAR-NK





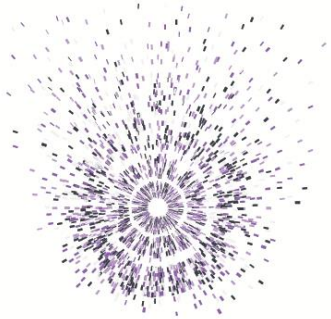

GI38
CRC14

CAR-NK



Sightera

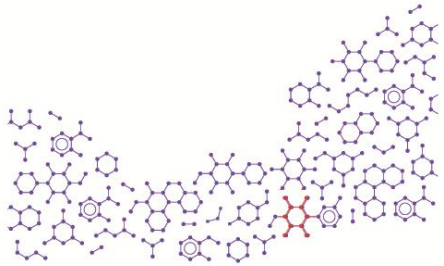
Ex vivo HT screen



AI

2 months

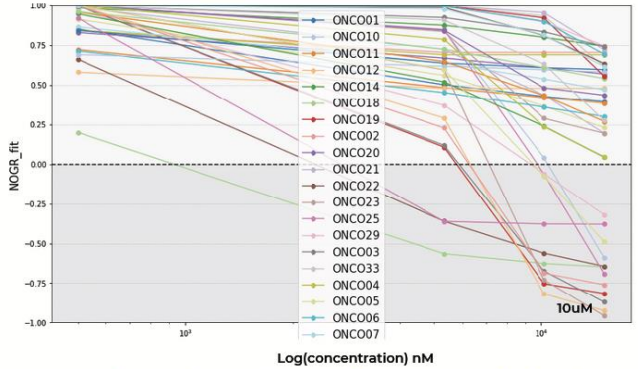
60 000 novel molecules



AI

2 months

Ex vivo efficacy



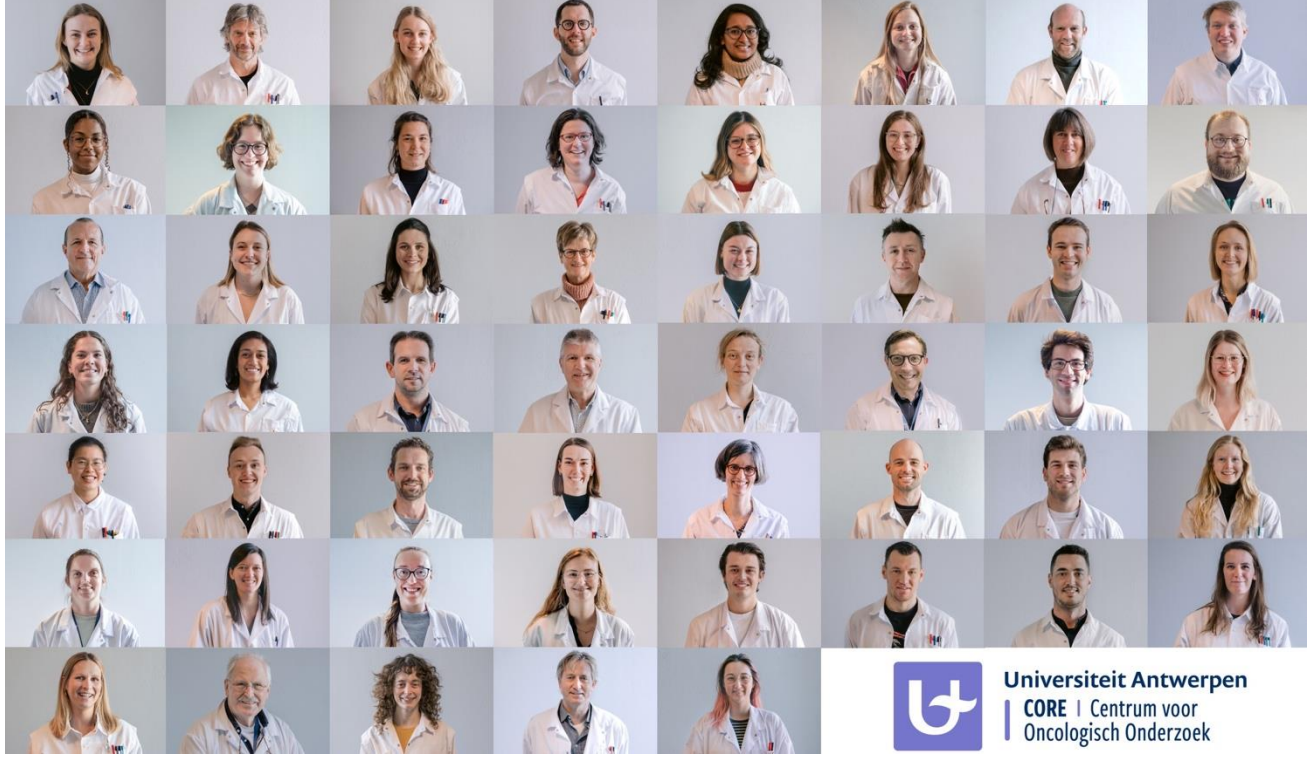
Use structural data of known inhibitors

Hit guided AI-based drug design

25/68 (37%) anti-tumor ‘hits’

Concluding remarks

- **Organoids offer unprecedented opportunities in CRC research and personalized medicine.**
- **They bridge the gap between lab discoveries and clinical care.**
- **Multidisciplinary collaboration to improve organoid research!**



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Prof. Komen

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dr. Gaillard

Lieselotte Iket

Thank you!

Questions?

If interested:

- LinkedIn of spin-off and spin-out
  - Orbits: https://www.linkedin.com/company/orbits-oncology/posts/?feedView=all
  - Drug Vision: https://www.linkedin.com/company/drugvision-ai/posts/?feedView=all
  - Sightera: https://www.linkedin.com/company/sightera-biosciences/posts/?feedView=all

- Futher reading:
  - van der Graaff D, Seghers S, Vanclooster P, Deben C, Vandamme T, Prenen H. Advancements in Research and Treatment Applications of Patient-Derived Tumor Organoids in Colorectal Cancer. Cancers (Basel). 2024 Jul 26;16(15):2671. doi: 10.3390/cancers16152671.
  - Seghers S, Le Compte M, Hendriks JMH, Van Schil P, Janssens A, Wener R, Komen N, Prenen H, Deben C. A systematic review of patient-derived tumor organoids generation from malignant effusions. Crit Rev Oncol Hematol. 2024 Mar;195:104285. doi: 10.1016/j.critrevonc.2024.104285.
  - Deben, C., Cardenas De La Hoz, E., Rodrigues Fortes, F. *et al.* Development and validation of the Normalized Organoid Growth Rate (NOGR) metric in brightfield imaging-based assays. *Commun Biol* **7**, 1612 (2024). https://doi.org/10.1038/s42003-024-07329-5
  - Le Compte M, De La Hoz EC, Peeters S, Fortes FR, Hermans C, Domen A, Smits E, Lardon F, Vandamme T, Lin A, Vanlanduit S, Roeyen G, Van Laere S, Prenen H, Peeters M, Deben C. Single-organoid analysis reveals clinically relevant treatment-resistant and invasive subclones in pancreatic cancer. NPJ Precis Oncol. 2023 Dec 8;7(1):128. doi: 10.1038/s41698-023-00480-y.
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