Tumour-Host Interactions in Liver Cancer of Childhood and Adults

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Director, Quantitative Biology Center (QBiC), University of Tübingen
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On behalf of:

Prof. Josep M Llovet THRIVE Coordinador
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Director, Master in Translational Medicine - *University of Barcelona*
Professor of Medicine, Director of Liver Cancer Program - *Icahn School of Medicine at Mount Sinai, NY, USA*

Funded by the European Union

Funded by the European Union under Grant Agreement No. 101136622.
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Why are we studying liver cancer?

Consortium

THRIVE is an EU-founded initiative that brings together a strong and multidisciplinary team with **13 partners**, from **8 countries**, with complementary expertise in **liver cancer** research and in the use of cutting-edge technologies



The THRIVE Consortium



1. Josep M Llovet (IDIBAPS, Barcelona)



2. Mathias Heikenwälder (EKUT, Tübingen)



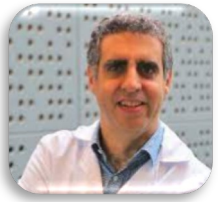
2. Sven Nahnsen (EKUT, Tübingen)



2. Manfred Claassen (EKUT, Tübingen)



3. Jessica Zucman-Rossi (UPCITE, Paris)



4. Manel Esteller (IJC, Barcelona)



5. Georg Zeller (LUMC, Leiden)



6. Carolina Armengol (IGPT, Barcelona)



7. Eran Elinav (WEIZMAN, Rehovot)



8. Jens Puschhof (DKFZ, Heidelberg)



9. Paola Cesaroni (Inn-Acta, IT)



10. Marko Korenjak (ELPA, Brussels)

EASL
The Home of Hepatology

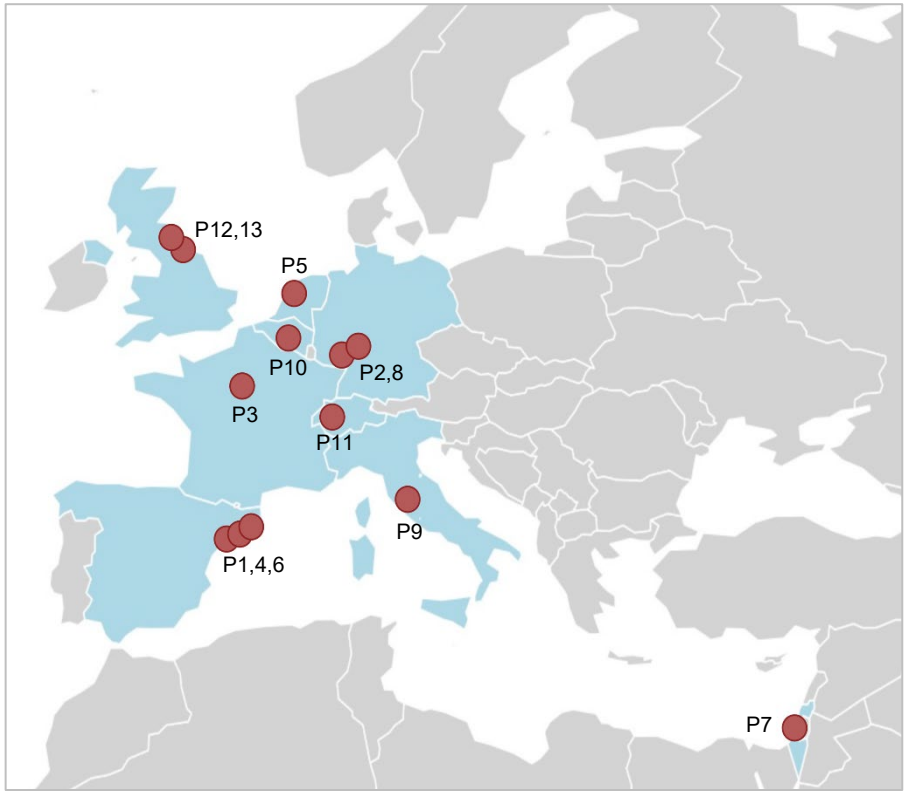
11. EASL (Switzerland)



12. Helen Reeves (UNEW, Newcastle)



13. Quentin Anstee (NUTH, Newcastle)



IDIBAPS Institut d'Investigacions Biomèdiques August Pi i Sunyer
Eberhard Karls Universität Tübingen
Université Paris Cité
Institut de Recerca Contra la Leucèmia Josep Carreras
Universiteit Leiden
IGTP
Weizmann Institute of Science
Inn·Acta
dkfz. Deutsches Krebsforschungszentrum in der Helmholtz-Gemeinschaft
ELPA European Liver Patients' Association
EASL The Home of Hepatology
Newcastle University
NHS The Newcastle upon Tyne Hospitals NHS Foundation Trust

The THRIVE Consortium

Partners (Institution; Lead)	Country
IDIBAPS – Hospital Clínic Barcelona; **Prof. Josep M Llovet – Coordinator**	Spain
University of Newcastle upon Tyne; **Prof. Helen Reeves**	UK
Newcastle upon Tyne Hospitals; **Prof. Quentin Anstee and Prof. Luise McDougall**	UK
DKFZ - Eberhard Karls Universität Tübingen; **Prof. Mathias Heikenwälder**	Germany
INSERM - Université Paris Cité; **Prof. Jessica Zucman-Rossi**	France
Institut de Recerca Contra la Leucemia Josep Carreras; **Prof. Manel Esteller**	Spain
EMBL - Leiden University Medical Centre; **Dr. Georg Zeller**	Germany
IGTP - Institut d'Investigació Germans Trias i Pujol; **Dr. Carolina Armengol**	Spain
Weizmann Institute of Science; **Prof. Eran Elinav**	Israel
DKFZ; **Dr. Jens Puschhof**	Germany
Innovation Acta; **Paola Cesaroni**	Italy
ELPA - European Liver Patients Association	Belgium
EASL - European Association for the Study of the Liver	Switzerland

State of the Art

- **Liver cancer** (**1M new cases per year)** is the 3rd **leading cause of cancer-related mortality** worldwide.[1]
- **Hepatocellular carcinoma** (HCC) is the most common type of liver cancer in **adults** (~90%) and **hepatoblastoma** (HB) in **children** (1.8 cases per million children/year).[2]

  ↳ Both are considered **poorly-understood cancers.**

- **50-60% of HCC** patients are exposed to **systemic therapies**, although only **~30% of patients respond**. [3,4]
- **HB is not cured in 30% of children** after surgical intervention and adjuvant chemotherapy.[5]

Overarching goal: **To enhance the outcome of paediatric and adult liver cancer patients by advancing the understanding of the disease, identifying biomarkers for current therapies, and developing novel treatments to overcome resistance.**

(1) Sung et al. CA Cancer J Clin 2021; (2) Feng et al. Cancer Commun 2019; (3) Llovet et al. Nat Rev Clin Oncol 2022; (4) Llovet et al. Nat Rev Dis Prim 2021; (5) Marin et al. Clin Res Hepatol Gastroenterol 2018

THRIVE specific objectives

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Aim #1. To understand the causative processes and key ***determinants of liver cancer*** development in adult patients and in children.



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(IDIBAPS, Barcelona)



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(UNEW, Newcastle)

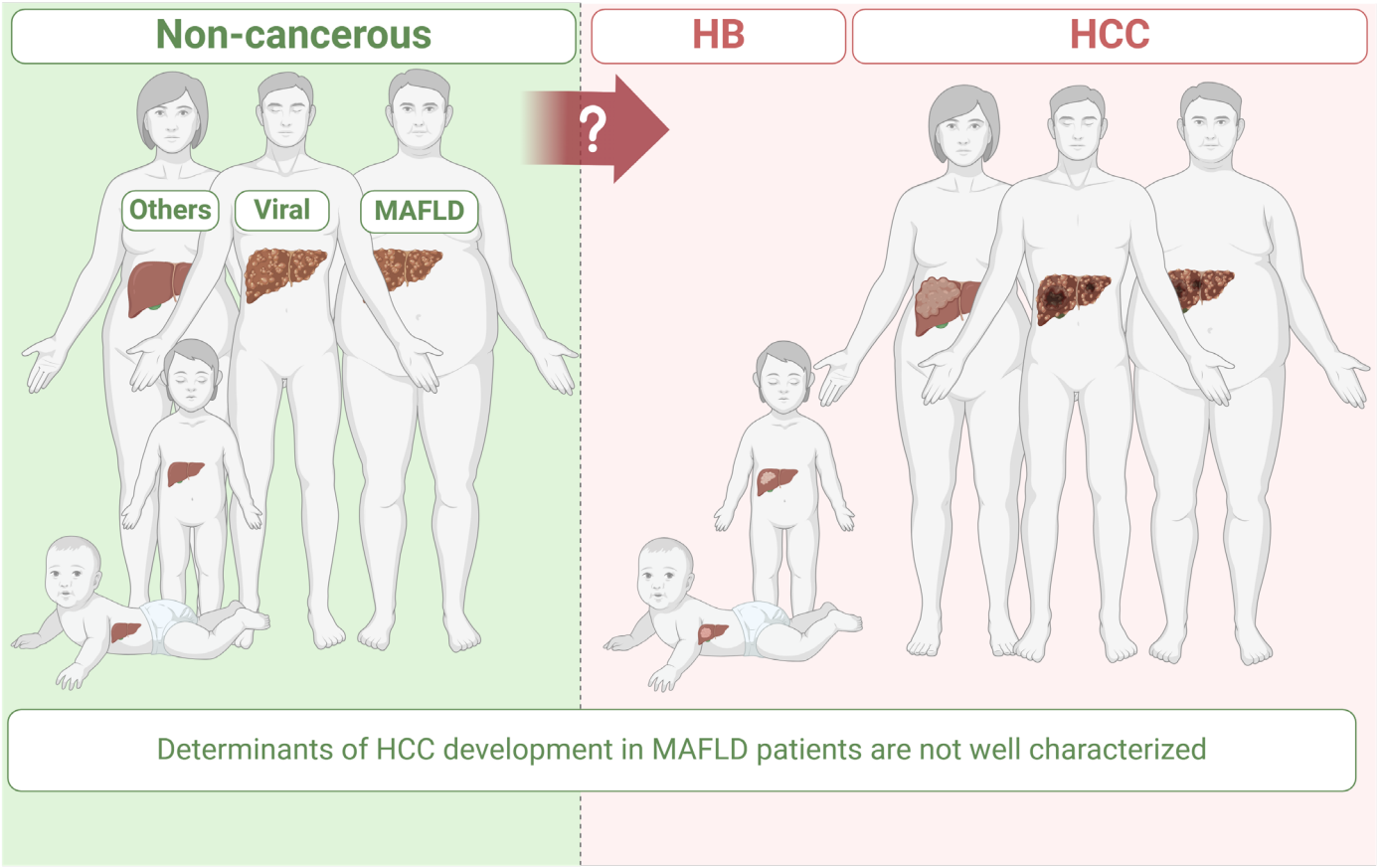


Quentin Anstee
(UNEW, Newcastle)

HB:



Carolina Armengol
(IGPT-CERCA, Barcelona)



THRIVE specific objectives

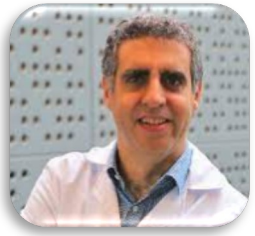
THRIVE specific objectives:

Aim #1. To understand the causative processes and key ***determinants of liver cancer*** development in adult patients and in children.

Aim #2. To ***decipher the molecular and cellular tumour–host interactions*** by understanding the immune and stroma cell population interactions, and exploring the liver cancer microbiome component.



Jessica Zucman-Rossi
(UPCITE, Paris)



Manel Esteller
(IJC-CERCA, Barcelona)



Eran Elinav
(WEIZMAN, IS)



Georg Zeller
(LUMC, Leiden)



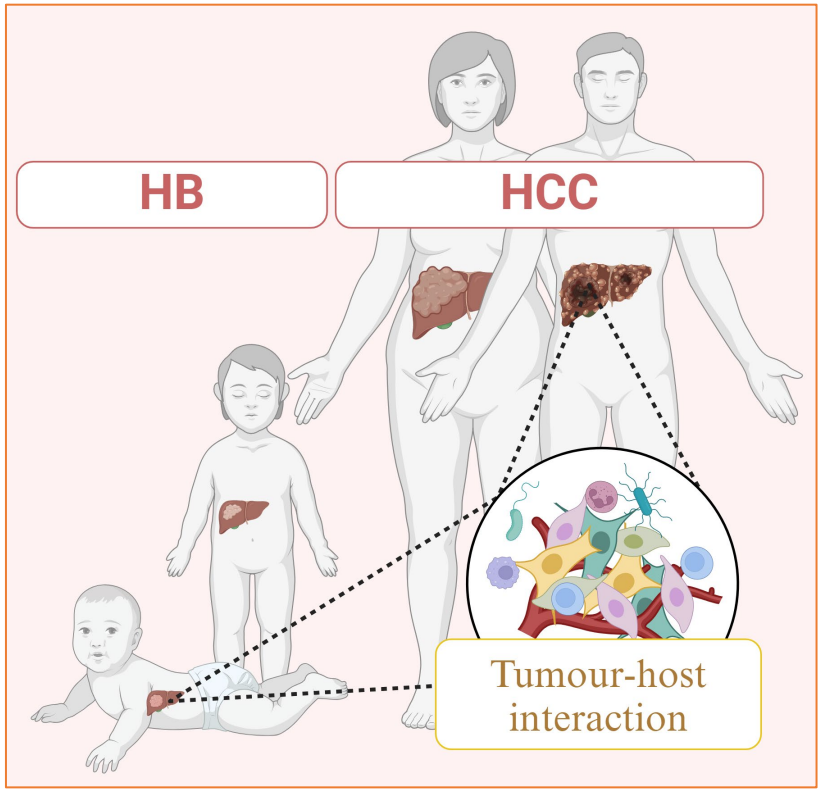
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Aim #3. To **develop reliable tools predicting response to treatment** by developing molecular biomarkers, and generating an AI-tool for guidance in decision making.



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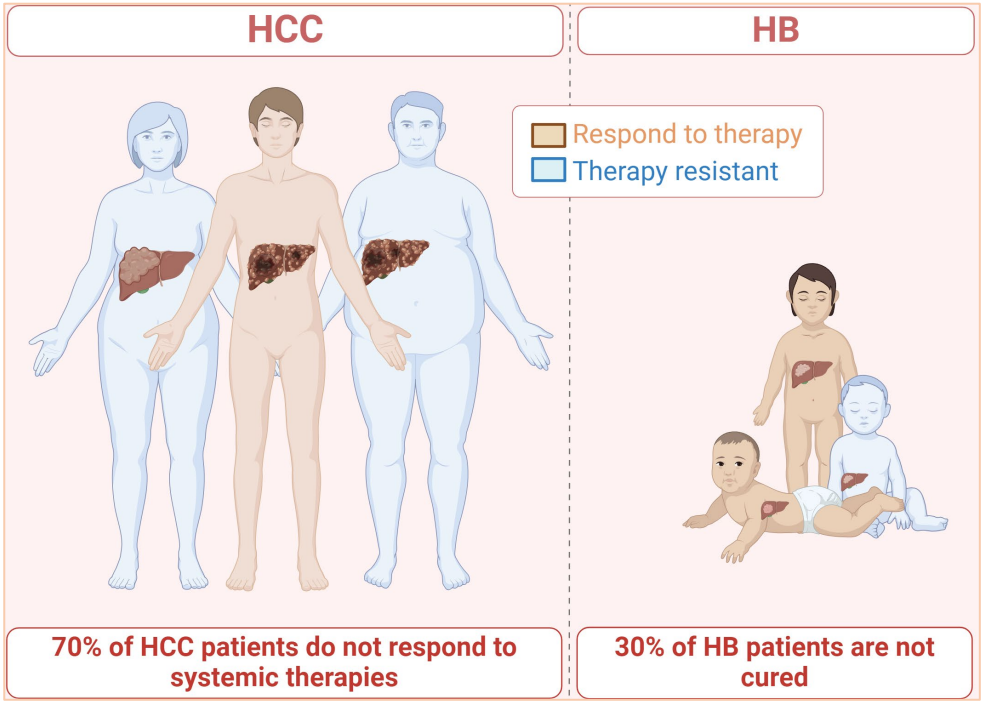
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THRIVE specific objectives

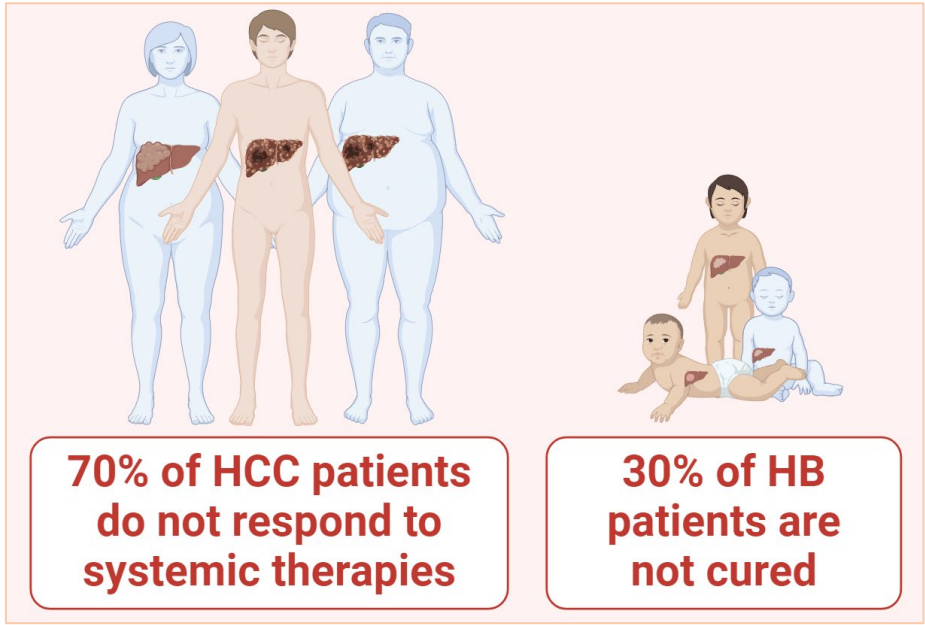
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Aim #3. To **develop reliable tools predicting response to treatment** by developing molecular biomarkers, and generating an AI-tool for guidance in decision making.

Aim #4. To propose **novel treatments** (socially acceptable & affordable), based on the evaluations of their efficacy and toxicity in HCC and HB ***patient-derived organoids (PDOs) and murine models***.




Mathias Heikenwälder (EKUT, Tübingen)


Eran Elinav (Weizman)


Jens Puschhof (DKFZ, Heidelberg)


Carolina Armengol (IGPT, Barcelona)

Project Aims

Overall goal: To enhance the outcome of paediatric and adult liver cancer patients by advancing the understanding of the disease, identifying biomarkers for current therapies, and developing novel treatments to overcome resistance.

We also aim to enhance the societal impact of our research, to promote FAIRness and Open Science, and to make health policy makers as well as healthcare professionals aware of the THRIVE results.

Aim #5. To **integrate** our discoveries with pre-existing resources, and support the development of the UNCAN.eu platform.



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Aim #5. To **integrate** our discoveries with pre-existing resources, and support the development of the UNCAN.eu platform.

Aim #6. To establish strategies to make health policy makers as well as health professionals aware of the THRIVE results.



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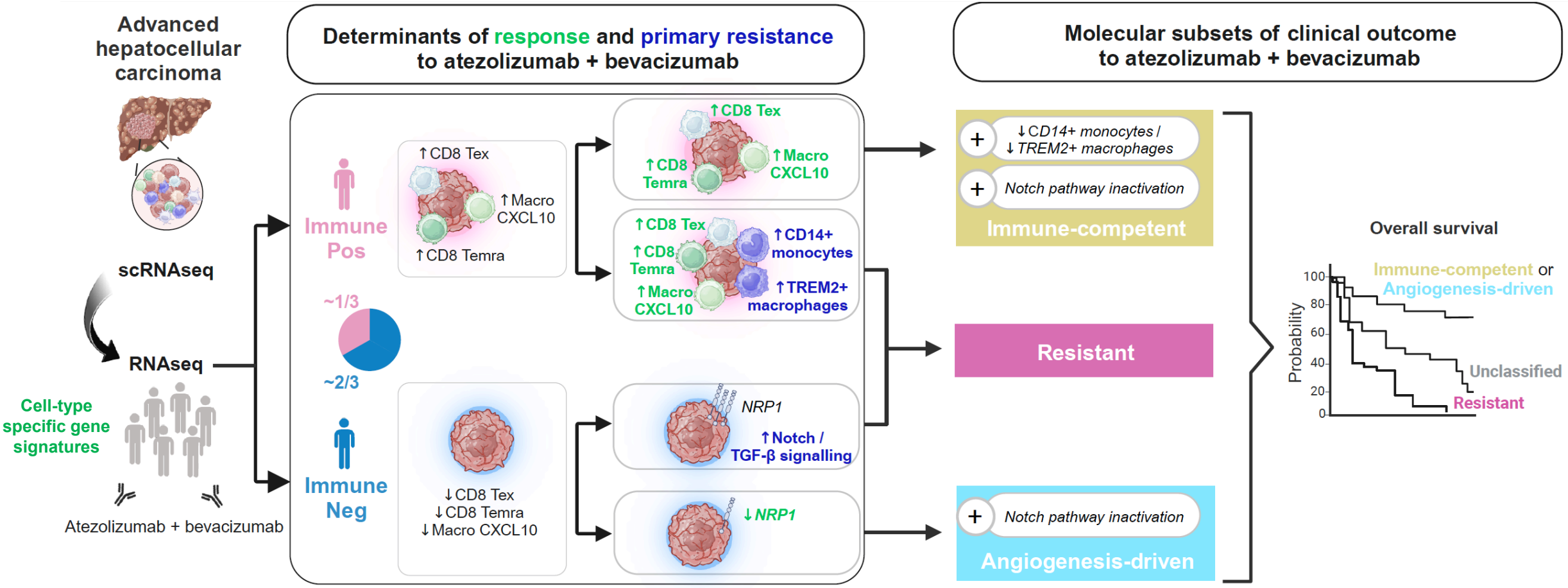


Paola Cesaroni
(Inn-Acta, IT)

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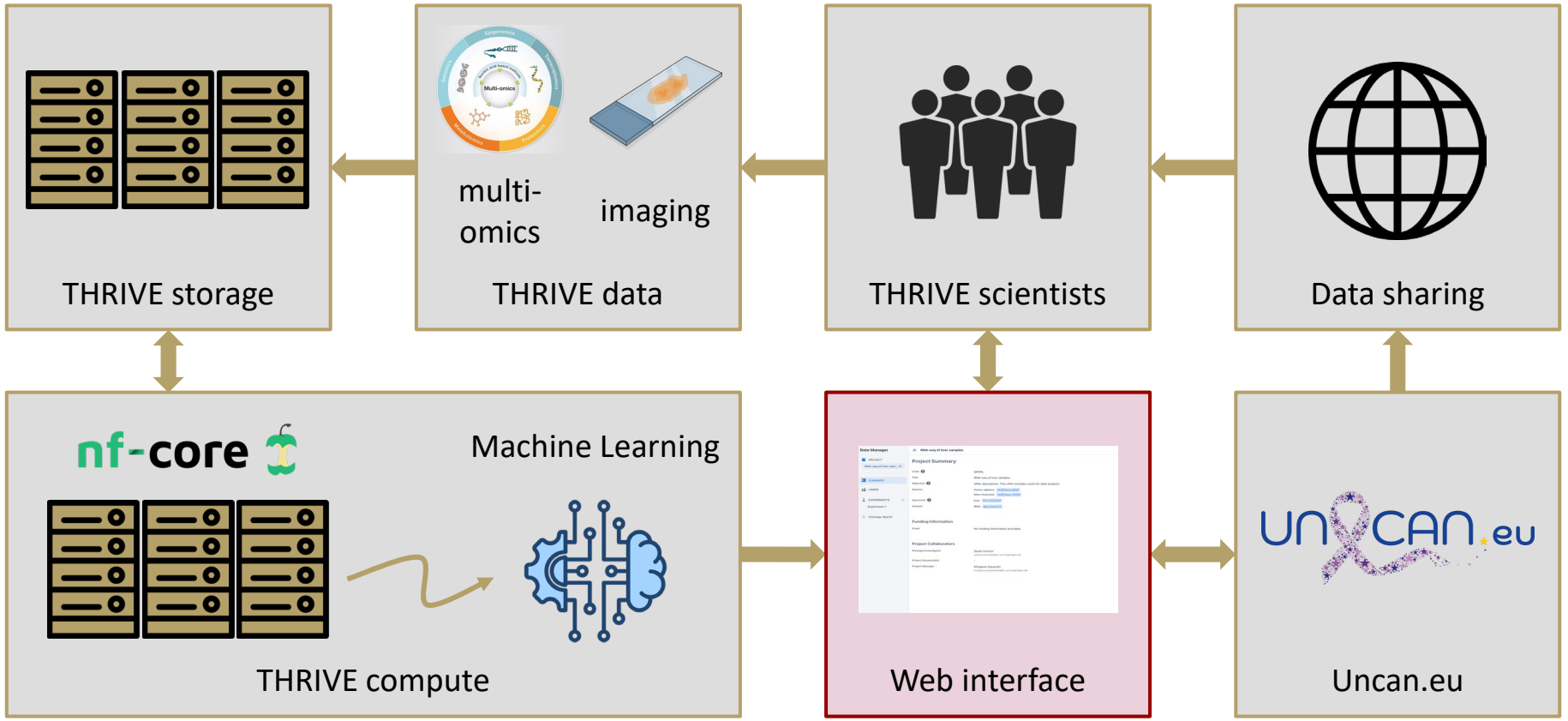
ELPA European Liver Patients' Association

Spatial transcriptomics of the tumor microenvironment discriminates inflamed tumors responsive or resistant to atezo+bev in patients with advanced HCC (Piqué-Gili et al,.)



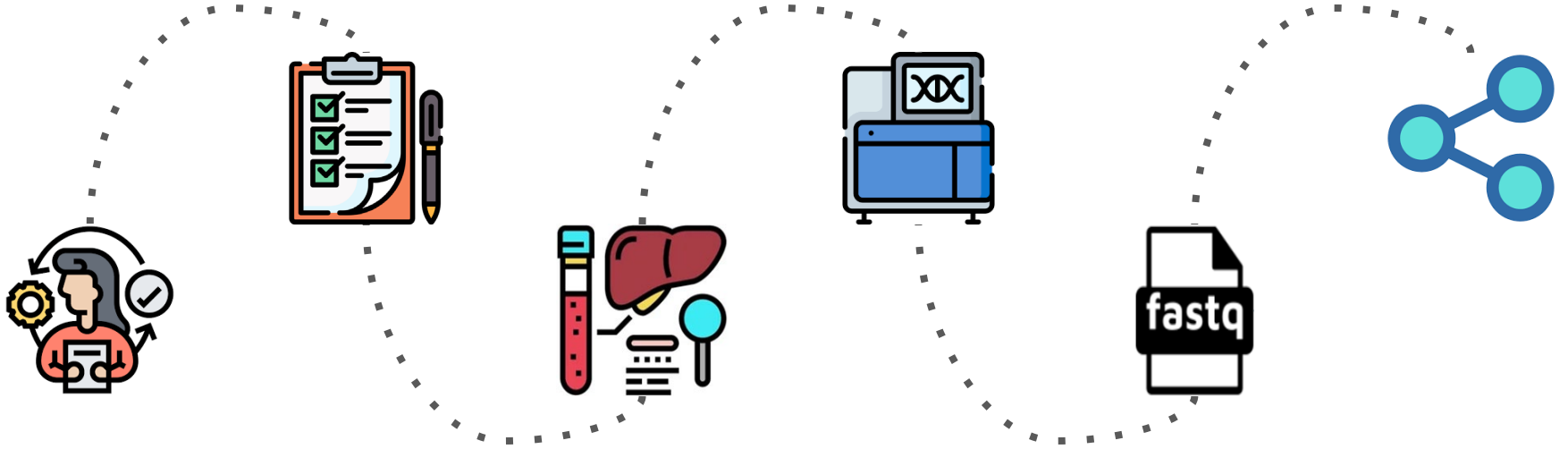
Cappuyns et al., JHEP 2025

Data Infrastructure



Web interface: Data manager

https://rdm.qbic.uni-tuebingen.de/



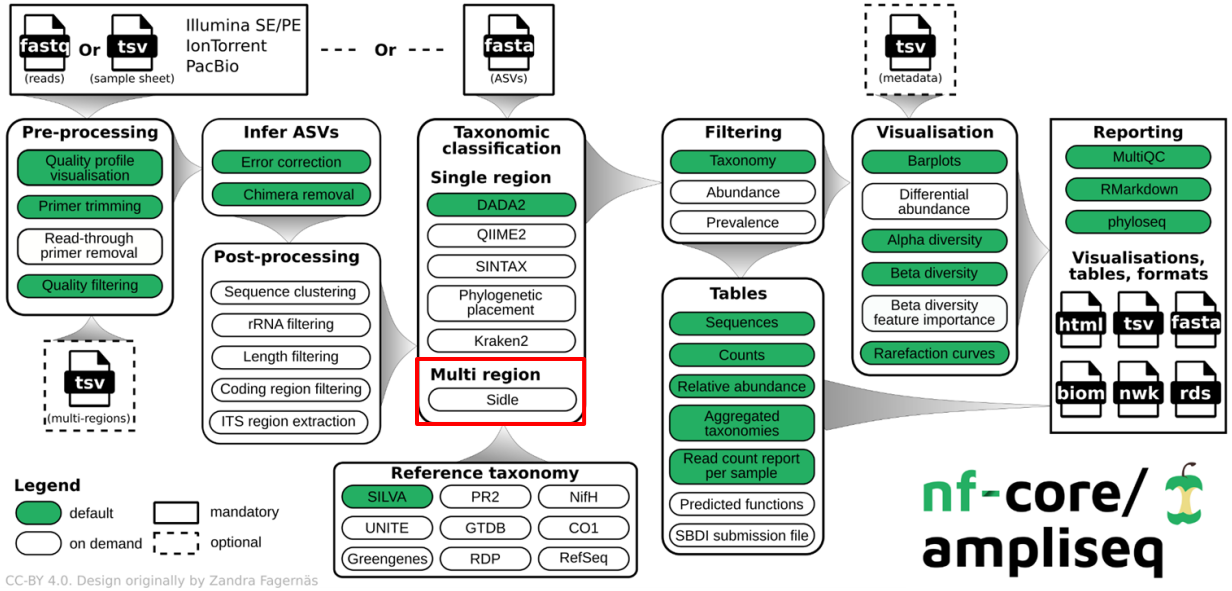
easy registration

project, experimental design, sample and measurement metadata

geo-redundant data storage

data sharing

Pipeline example: Combining 16S rRNA gene variable regions via Sidle



Seamless integration into **nf-core/ampliseq**

nf-core/ampliseq v2.12.0: https://nf-co.re/ampliseq/2.12.0/
SMURF: https://doi.org/10.1186/s40168-017-0396-x
Sidle: https://doi.org/10.1101/2021.03.23.436606

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Multiple region analysis with Sidle

Instead of relying on one short amplicon, scaffolding multiple regions along a reference can improve resolution over a single region. This method applies Sidle (SMURF Implementation Done to acceLerate Efficiency) within QIIME2 with Silva (see licence) or Greengenes database.

For example, multiple variable regions of the 16S rRNA gene were sequenced with various primers and need to be unified. This leads to one unified abundance and taxonomy profile over all variable regions. However, ASV sequences are only available separately, there is no reconstruction of complete de-novo sequences feasible.

Information about sequencing data via `--input`, region primers length information via `--multiregion`, and a taxonomic database via `--sidle_ref_taxonomy` or `--sidle_ref_tax_custom` is required.

```
--input "samplesheet_multiregion.tsv"  --multiregion "regions_multiregion.tsv" --sidle_ref_taxonomy "silva=128"
```

The region information file can be tab-separated (.tsv), comma-separated (.csv), or in YAML format (.yml/.yaml) and can have two to four columns/entries with the following headers:

Column	Description
region	Unique region identifier
region_length	Minimum region length, sequences are trimmed and shorter ones are omitted
FW_primer	Forward primer sequence
RV_primer	Reverse primer sequence

For example, the tab-separated `regions_multiregion.tsv` may contain:

region	FW_primer	RV_primer	region_length
region1	TGGCGAACGGGTGAGTAA	CCGTGTCTCAGTCCCARTG	145
region2	ACTCCTACGGGAGGCAGC	GTATTACCGCGGCTGCTG	135
region3	GTGTAGCGGTGRAATGCG	CCCGTCAATTCMTTTGAGTT	200
region4	GGAGCATGTGGWTTAATTCGA	CGTTGCGGGACTTAACCC	115
region5	GGAGGAAGGTGGGGATGAC	AAGGCCCGGGAACGTATT	150

https://nf-co.re/ampliseq/2.12.0/docs/usage/#multiple-region-analysis-with-sidle

THRIVE

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