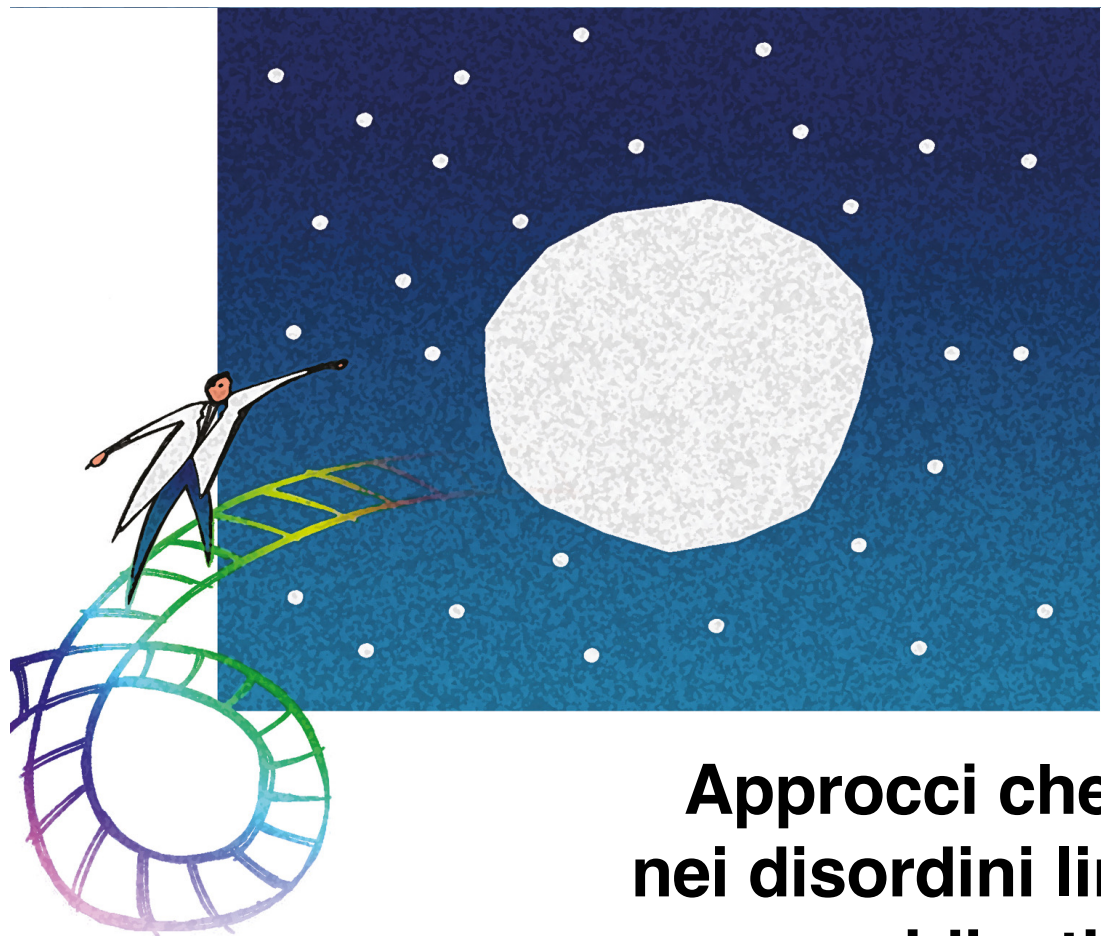




The young side of **LYMPHOMA**

gli under 40 a confronto

Reggio Emilia, Hotel Mercure Astoria
2-3 ottobre 2026

Approcci chemogenomici nei disordini linfoproliferativi recidivati/refrattari

Luca Pagliaro, MD, PhD

Ematologia e CTMO, A.O.U. Parma

Translational Hematology and Chemogenomics (THEC), Università di Parma

THEC
TRANSLATIONAL HEMATOLOGY AND CHEMOGENOMICS



**SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA**
Azienda Ospedaliero - Universitaria di Parma



**UNIVERSITÀ
DI PARMA**

Disclosures of Luca Pagliaro

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche					x		
Astra Zeneca							x
Incyte					x		

Outline

1.  Unmet Need in Precision Medicine
2.  Where Do We Stand Today
3.  Lymphoid Malignancies Through a Functional Lens
4.  From *ex vivo* Testing to Clinical Decisions
5.  Modeling Lymphoma: The Limits of *ex vivo* Testing
6.  Conclusion

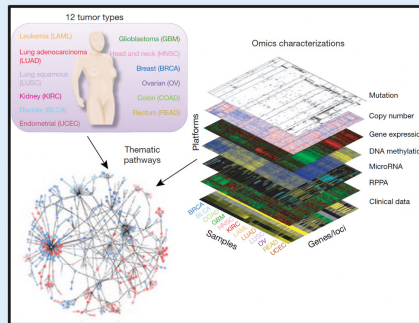
Domanda 1

Che cosa si intende per 'cancer dependency'?

- A. Una mutazione che permette di associare un tumore a un farmaco mirato.
- B. La necessità delle cellule tumorali di una funzione biologica specifica per sopravvivere o proliferare.
- C. La presenza di una proteina espressa maggiormente nel tumore rispetto al tessuto sano.
- D. La capacità delle cellule tumorali di sviluppare resistenza dopo un trattamento.

Changing the Paradigm in Cancer Treatment

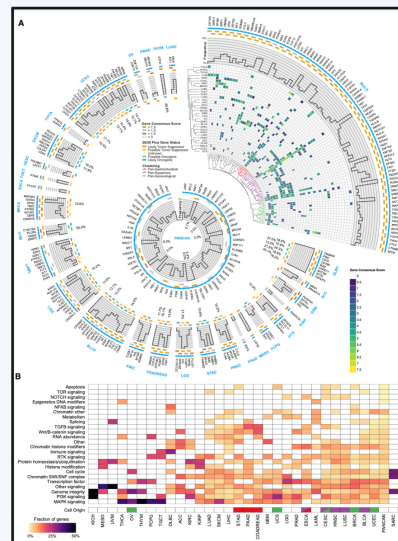
The Cancer Genome Atlas (TCGA-ICGC) (2010)



- 500 driver genes
- 12 common tumor types
- Definition of "mutational landscape"

Hudson et al. Nature, 2010
TCGA Res Network. Nat Gen, 2013

PanCancer Driver Genes (2018)



- 299 cancer driver genes
- Shared across cell types
- 57% tumors harbor potentially actionable mutations

Bailey et al. Cell, 2018

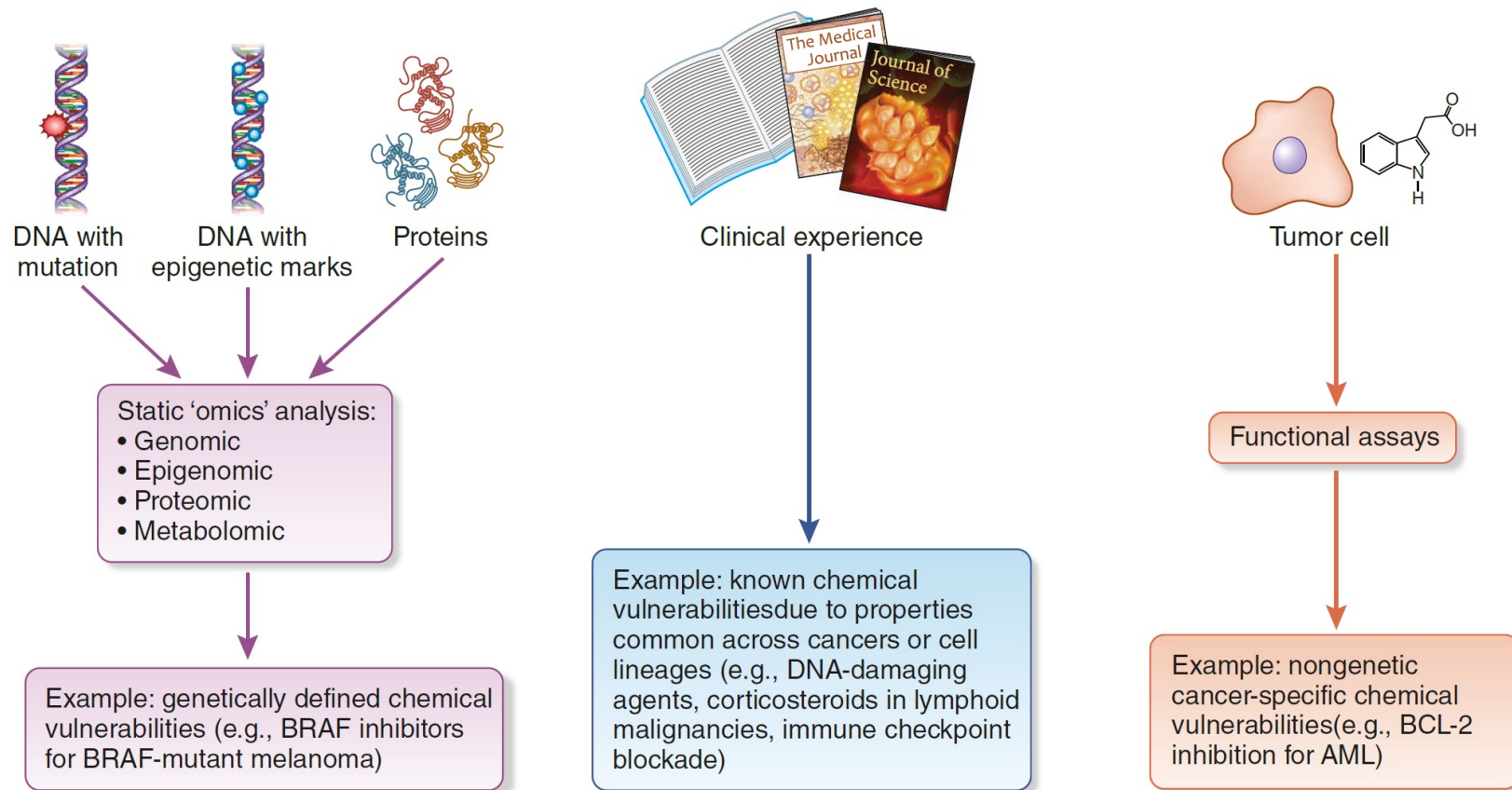
DepMap (2018-ongoing)



- 2000 models, 30 lineages
- Gene mutations represent the minority of cancer dependencies
- Gene expression emerged as best predictor of dependencies

Dharia et al. Nat Gen, 2021
Arafah et al. Nat Rev Can, 2025

From a Static to a Functional Approach

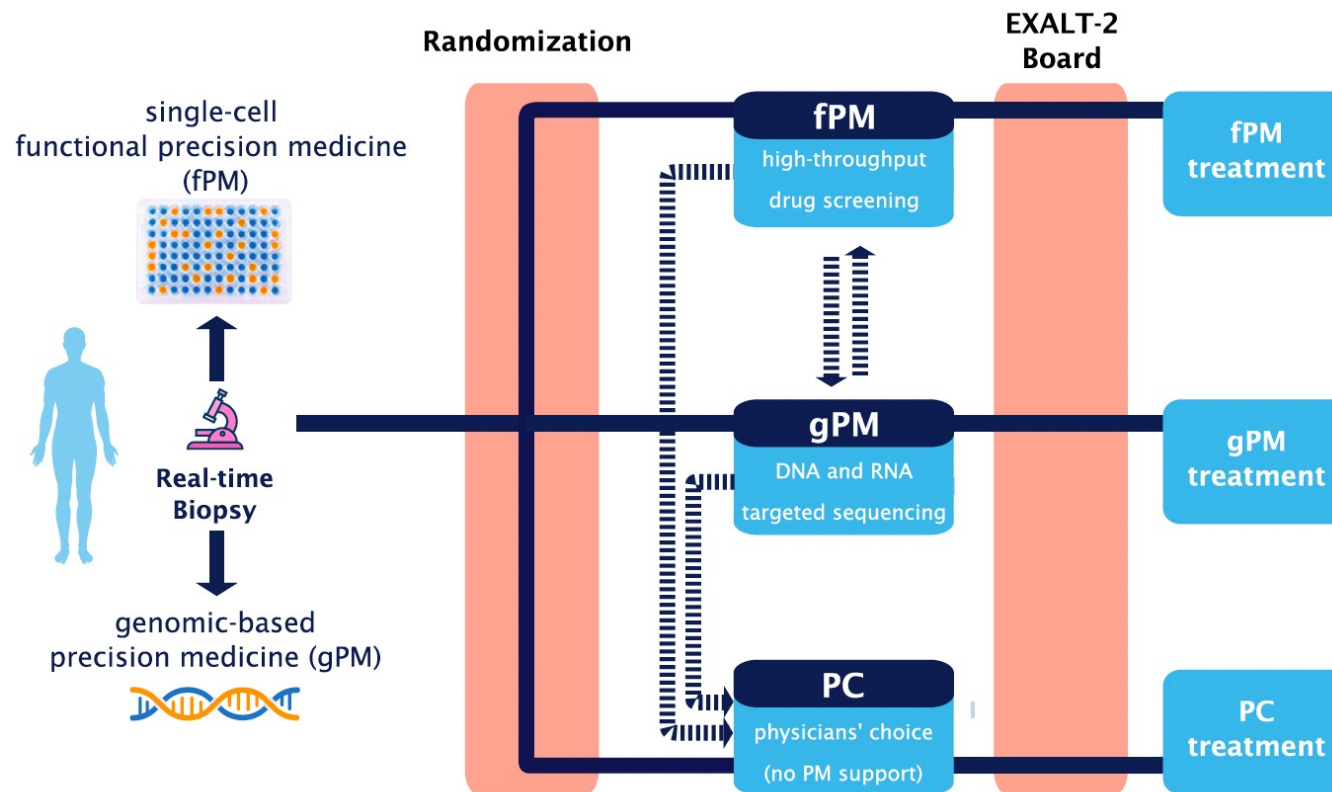


Domanda 2

Quale approccio permette una caratterizzazione più completa delle dipendenze tumorali rilevanti per la sensibilità ai farmaci in un linfoma?

- A. Analisi delle alterazioni genomiche associate a bersagli terapeutici (“one gene-one drug”)
- B. Misurazione della sensibilità farmacologica mediante saggi funzionali *ex vivo*.
- C. Classificazione del tumore mediante istologia e immunofenotipo.
- D. Integrazione di profili molecolari, saggi funzionali, contesto istopatologico e altre caratteristiche “omiche”.

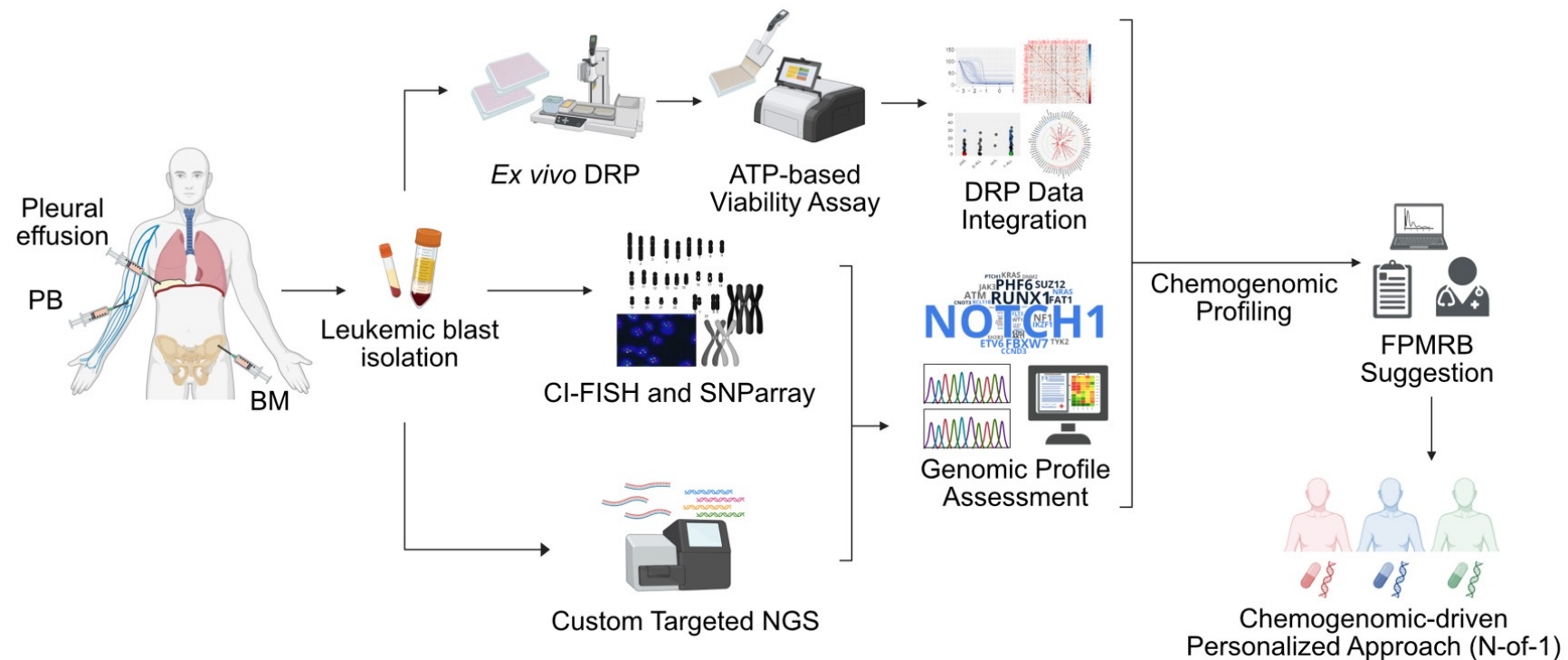
Beyond the «One-Gene/One-Drug» Approach



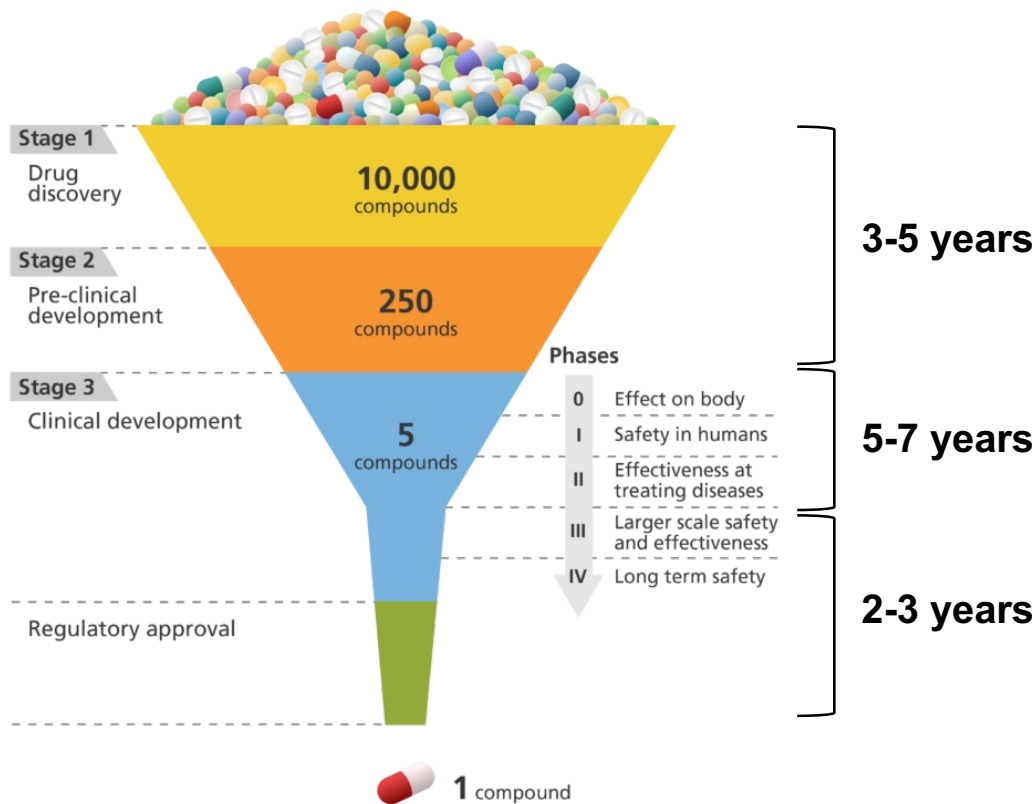
Functional Precision Medicine: Putting Drugs on Patient Cancer Cells and Seeing What Happens



Anthony Letai



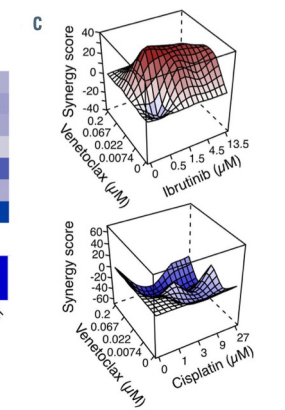
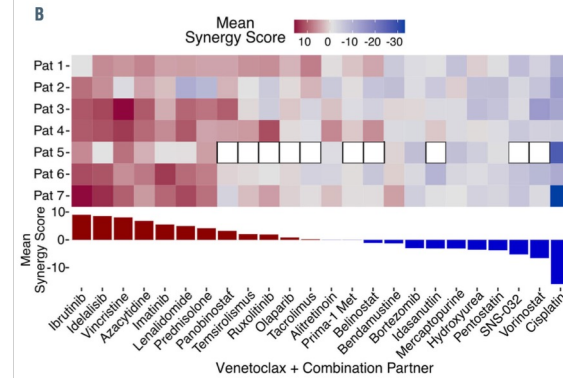
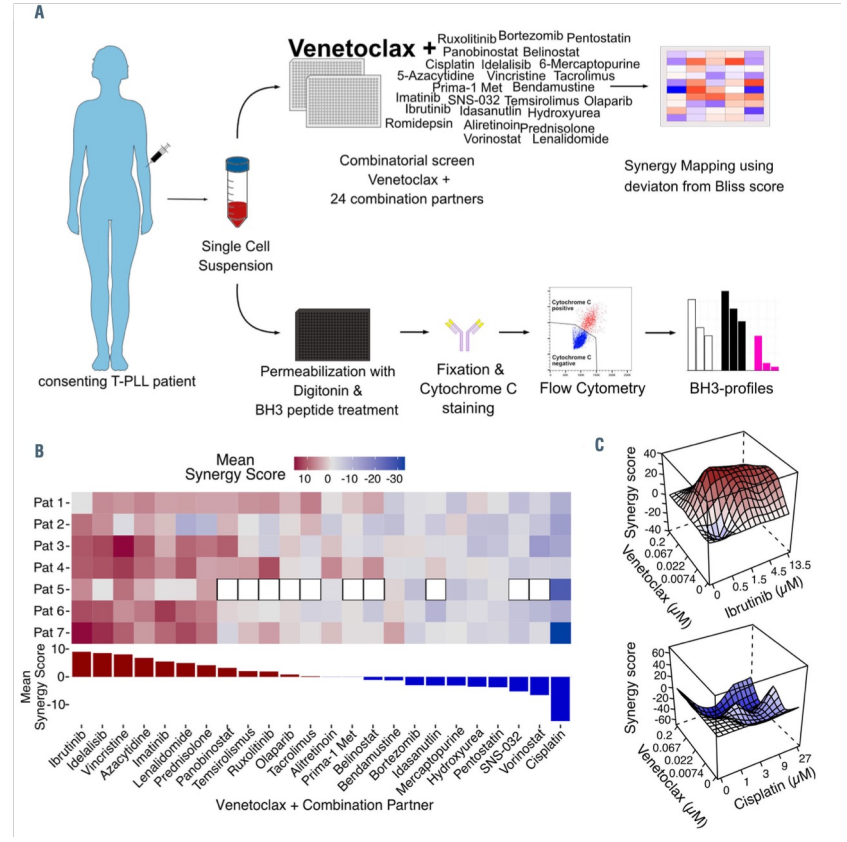
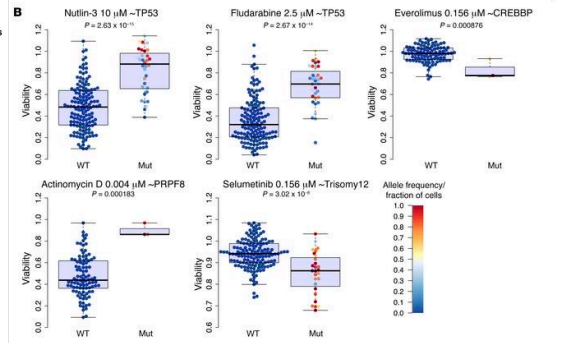
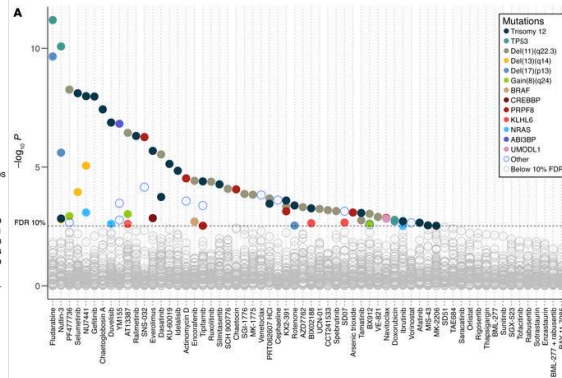
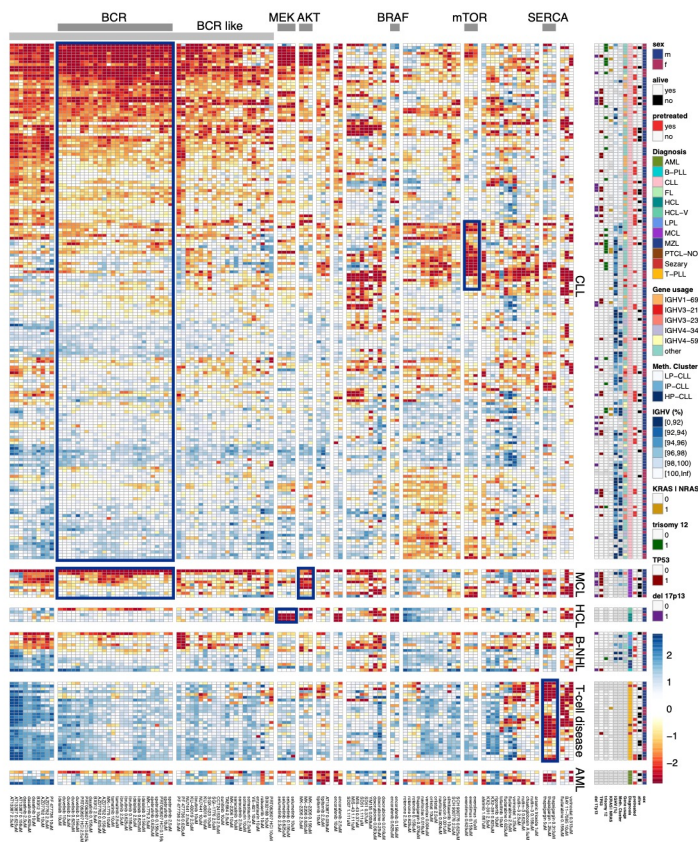
Functional Precision HEM/ONC: Testing Tumors with Drugs to Identify Vulnerabilities



Ex-vivo Drug Sensitivity & Multi-Omics

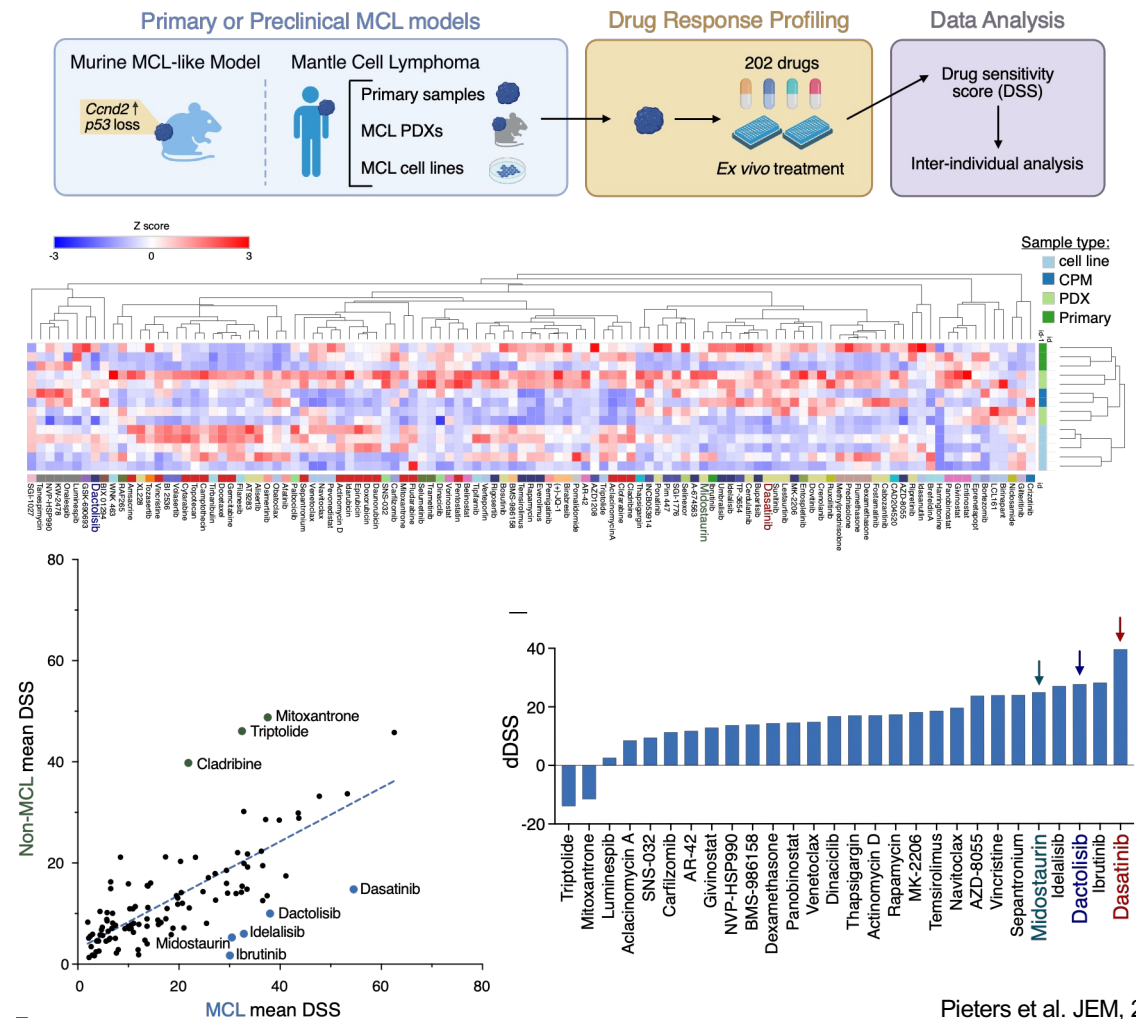
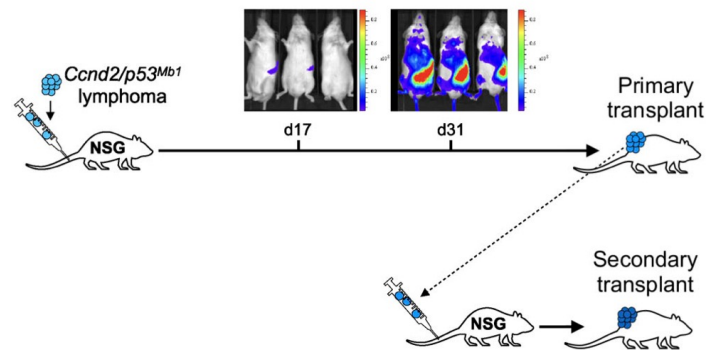
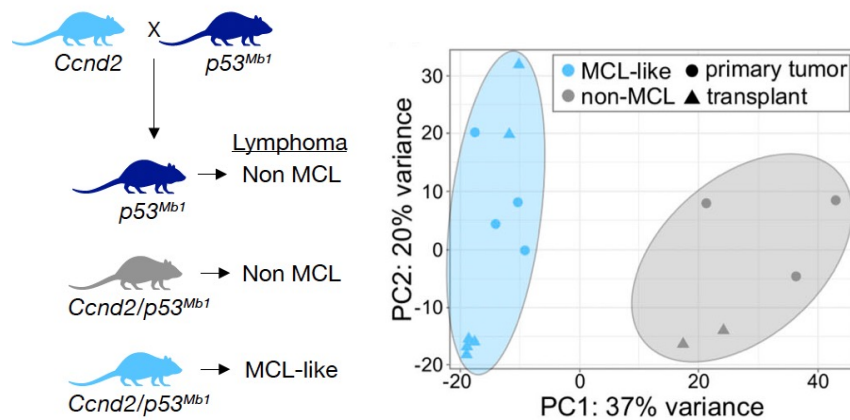
- Cover natural genetic heterogeneity
- Test multiple drugs on the same tumor in parallel
- Probe individual pathway dependencies
- Discovery of phenotypically important molecular subtypes
- Repurposing / Combination opportunities
- Insight/ New clinical Trial "n-of-1" approaches
- Application in precision oncology. Prospective clinical trials

Ex vivo DRP Identifies Functional Classification and Novel Vulnerabilities in LPD



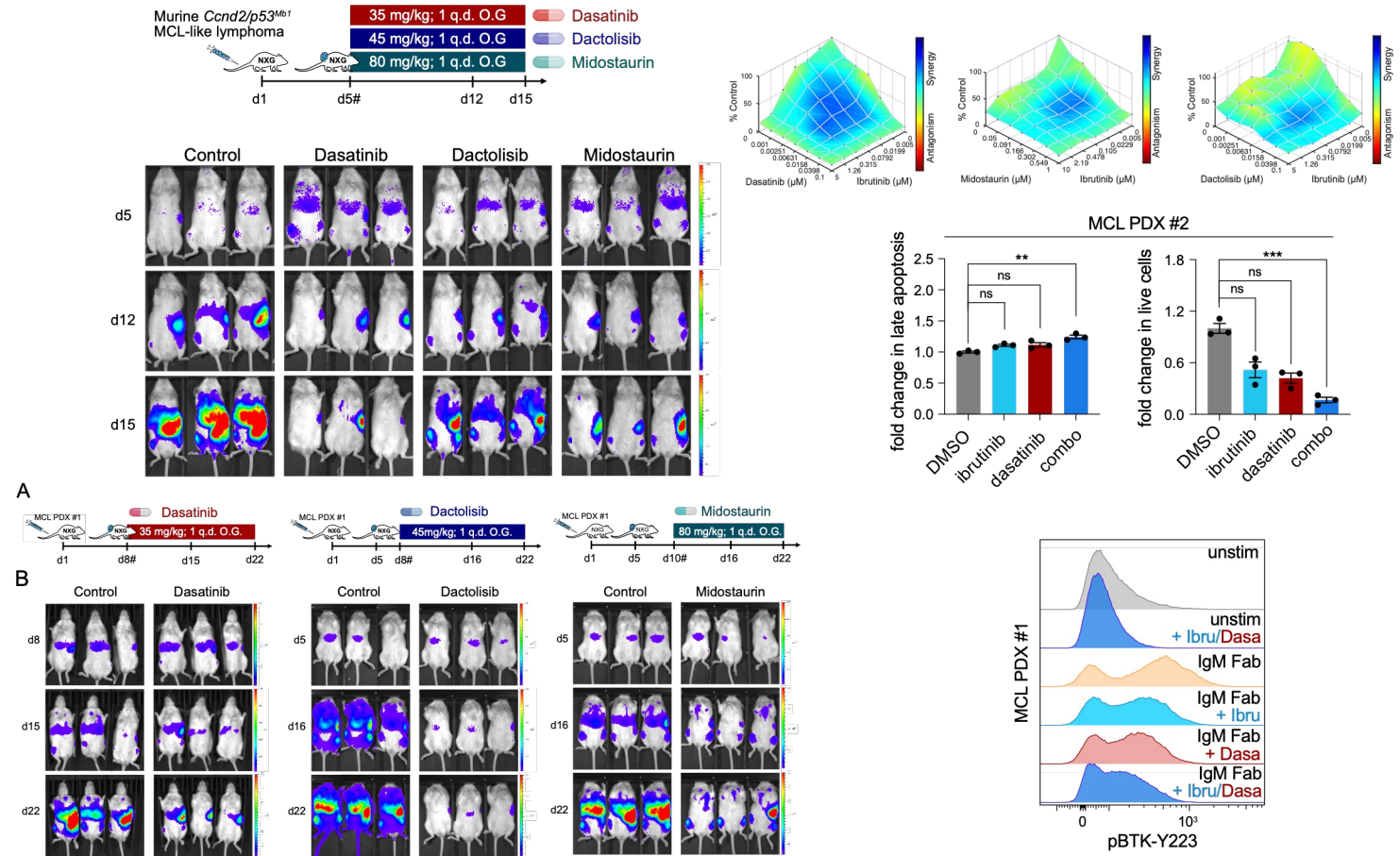
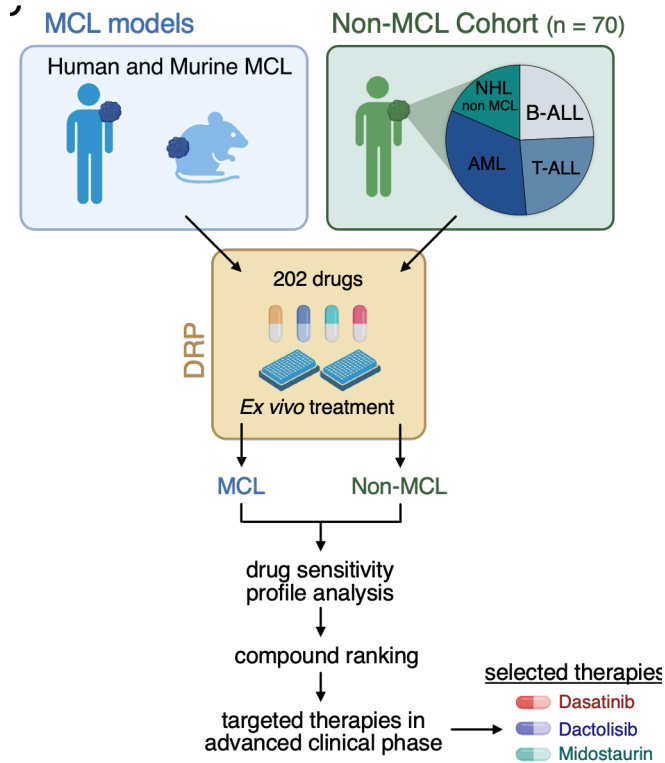
Dietrich et al. J Clin Invest, 2018
 Boidol et al. Blood, 2017
 Kornauth et al. Haematologica, 2021

Drug screening identifies candidate vulnerabilities in MCL

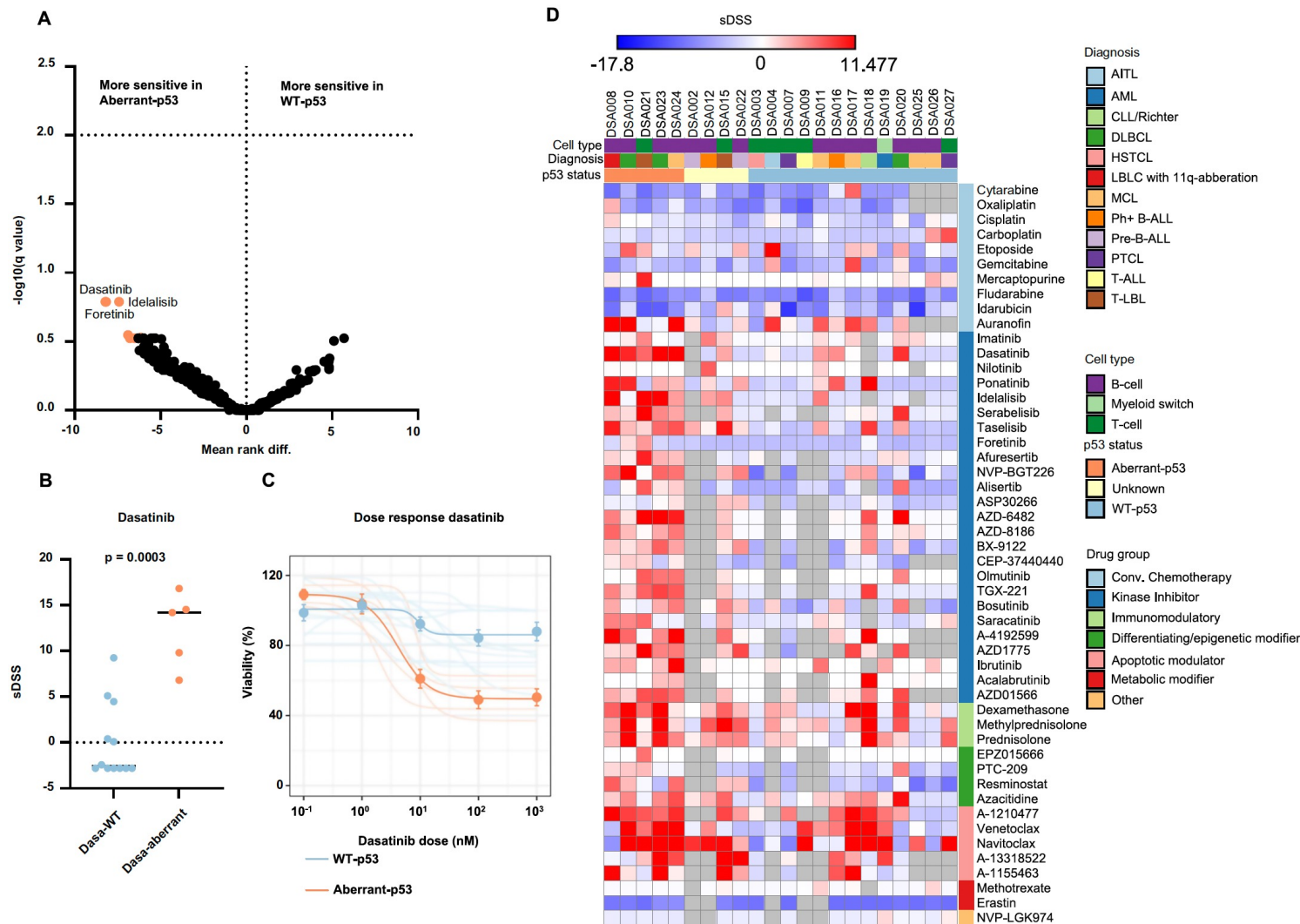


Pieters et al. JEM, 2019
Pagliaro et al. Cell Death Dis, under review

Validation across complementary MCL models



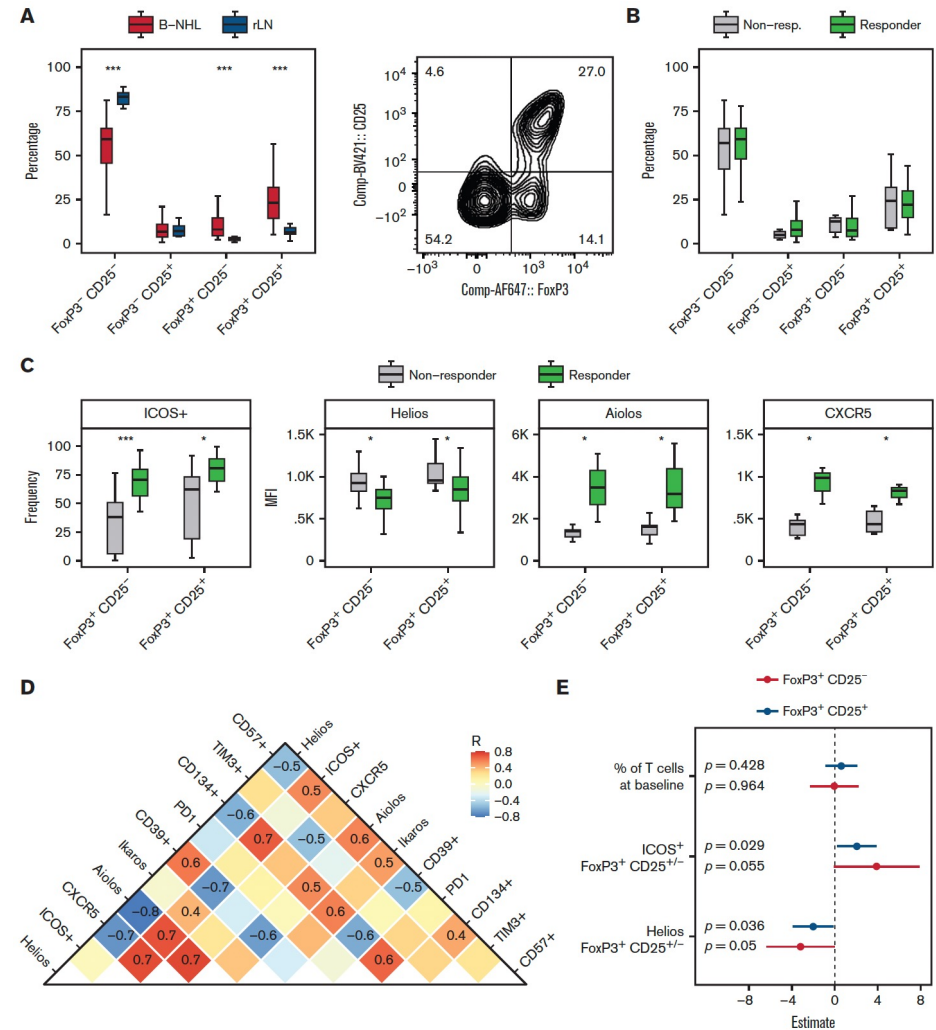
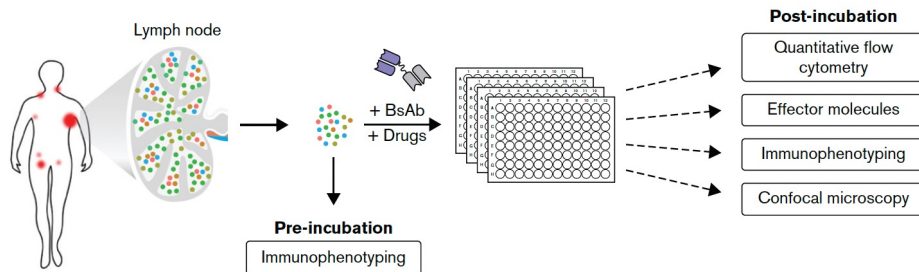
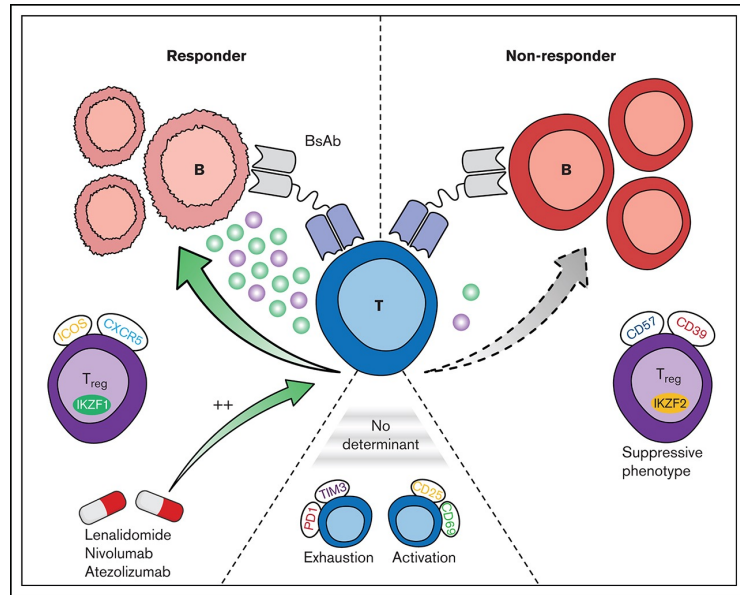
p53-linked Vulnerabilities in R/R Lymphoid Malignancies



The diagram illustrates a multi-omic workflow for studying lymph node cell types. It begins with a human figure highlighting lymph node locations, which are then magnified to show a lymph node containing various cell types. This leads to a t-SNE plot of scRNA-seq data. Three clusters are identified and analyzed by flow cytometry, showing dot plots for cell counts. These clusters then undergo three parallel analyses: Drug screening (resulting in a viability graph for B1, B2, B3), DNA sequencing (resulting in sequence alignment for B1, B2, B3), and Protein expression (resulting in a density plot of mean expression for B1, B2, B3).



NHL models for immunotherapy determinants of response

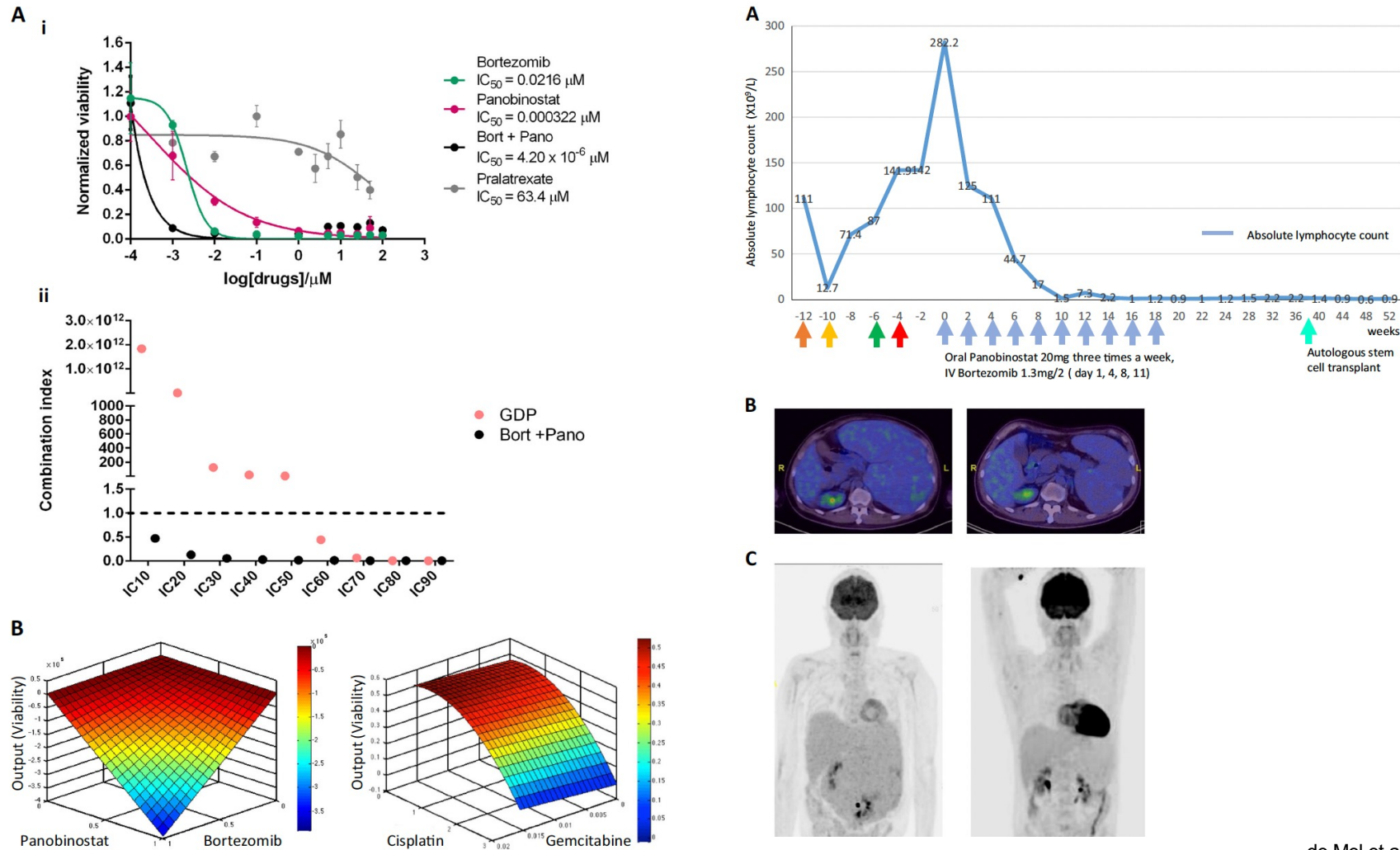


Domanda 3

“N-of-1 trial”, di cosa si tratta?

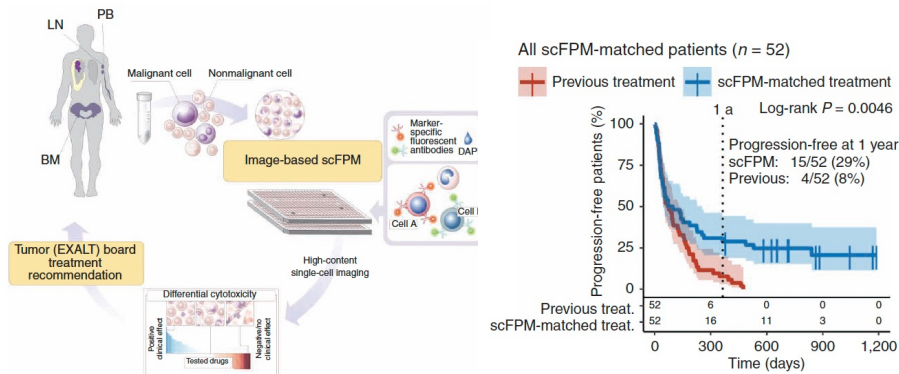
- A. Uno studio che valuta un solo farmaco in molti pazienti affetti dalla stessa patologia.
- B. Uno studio sperimentale condotto su un singolo paziente, indipendentemente dalla patologia, che funge da controllo di sé stesso.
- C. Uno studio dedicato a una sola alterazione molecolare in più patologie differenti.
- D. Una descrizione della risposta eccezionale di un paziente.

From *ex vivo* Testing to Clinical Decisions in NHL



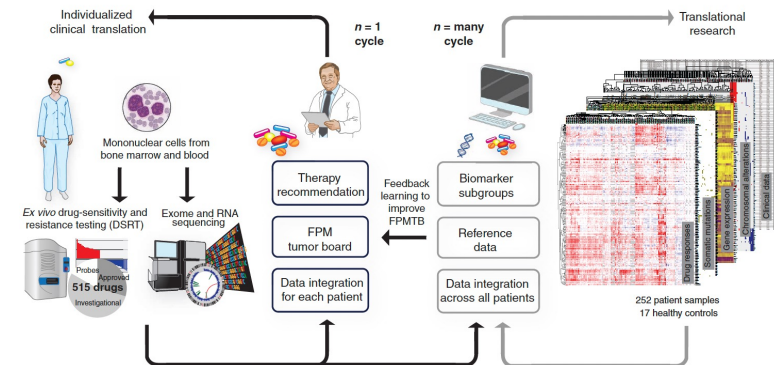
Rethink HEM/ONC Clinical Trials through FPM

EXALT-1



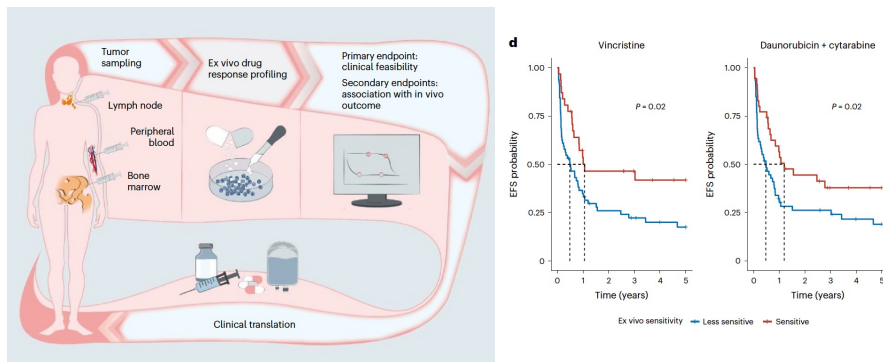
Kornauth et al. Can Disc, 2022

FIMM, Helsinki



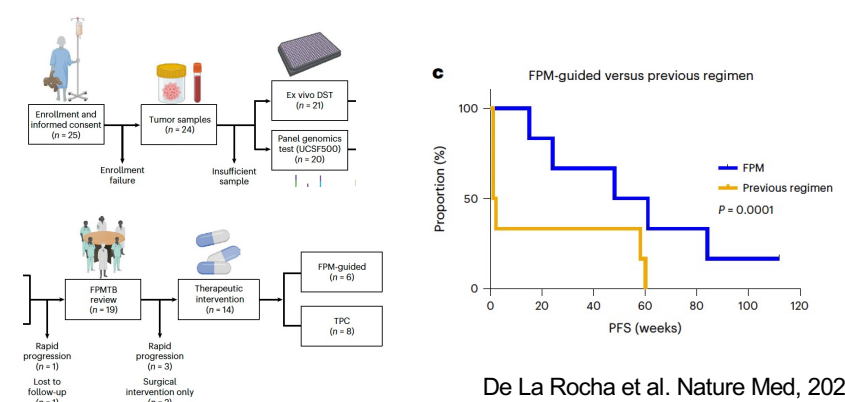
Malani et al. Can Disc, 2022

SMARTrial



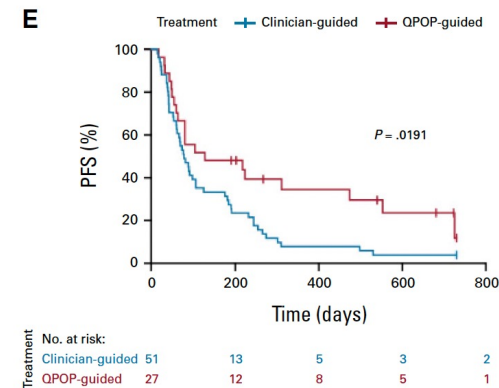
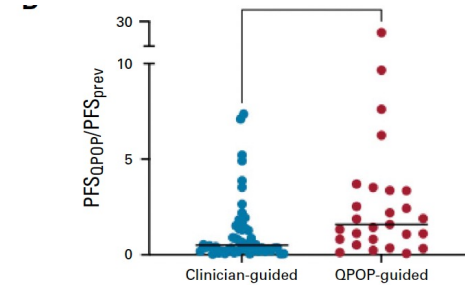
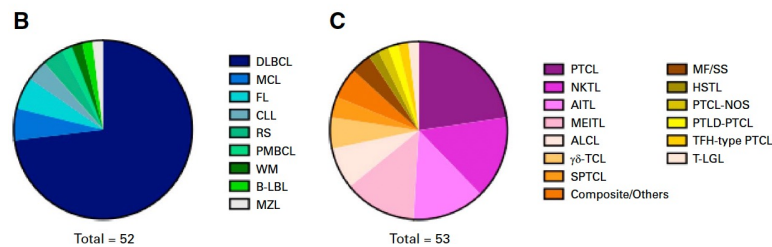
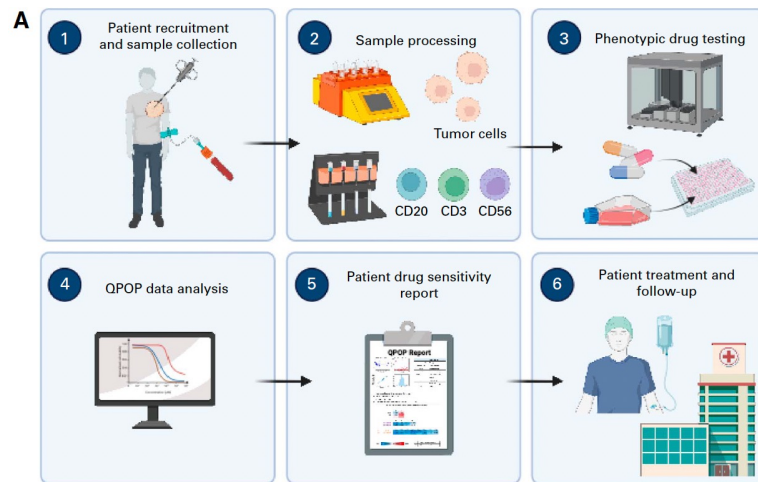
Liebers et al. Nature Canc, 2023

FIU, Westchester, FL

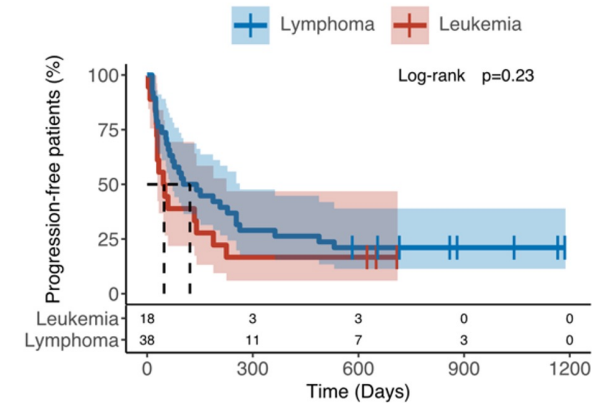
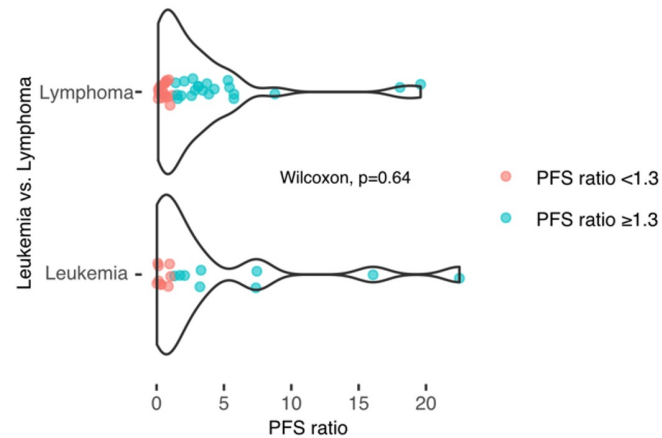
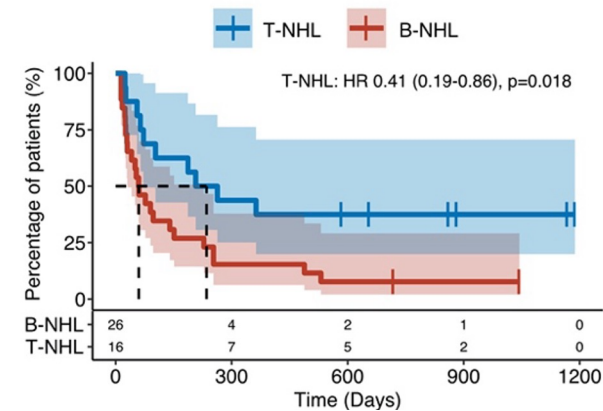
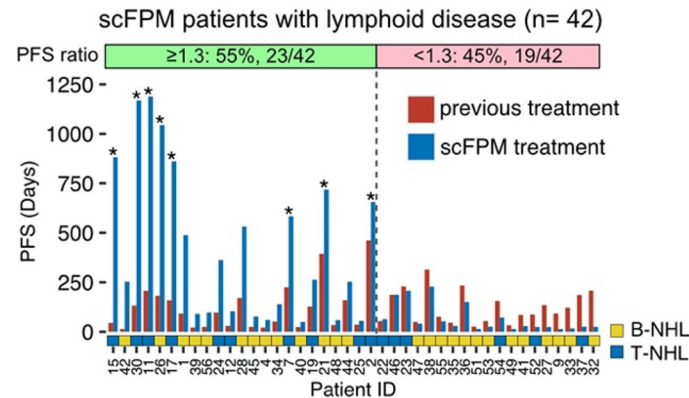


De La Rocha et al. Nature Med, 2024

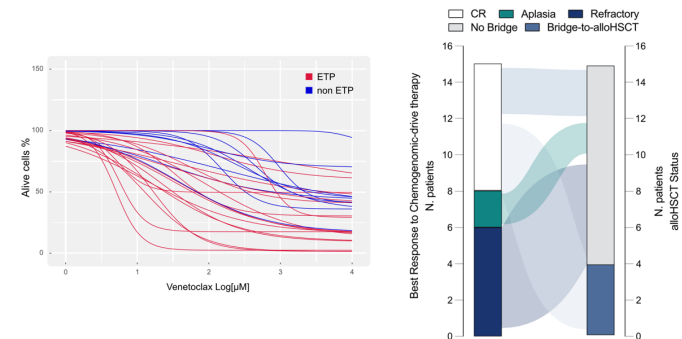
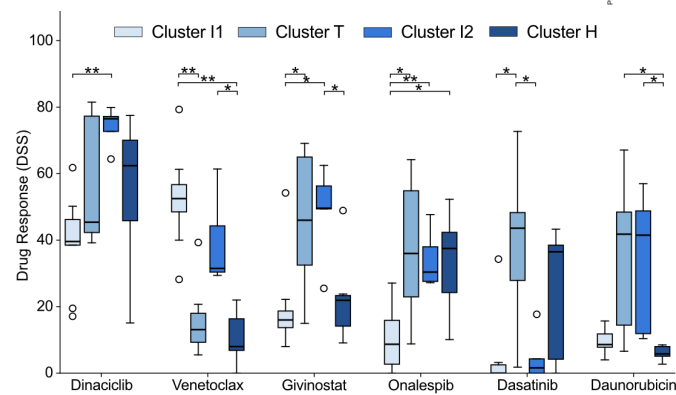
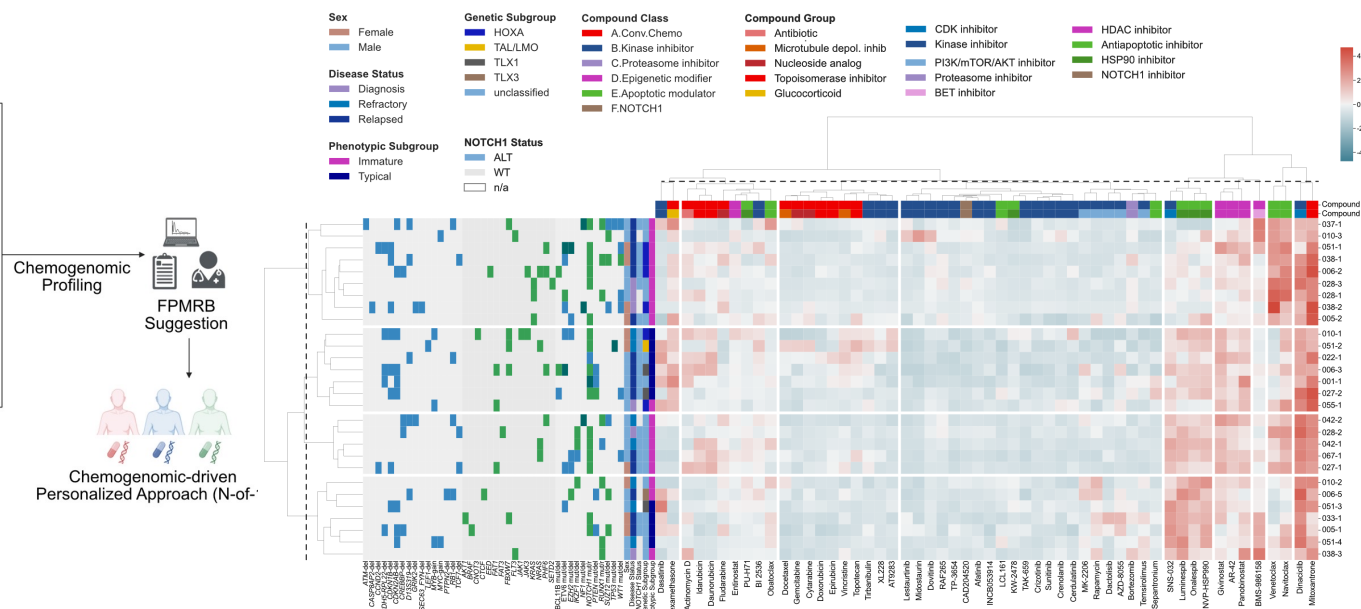
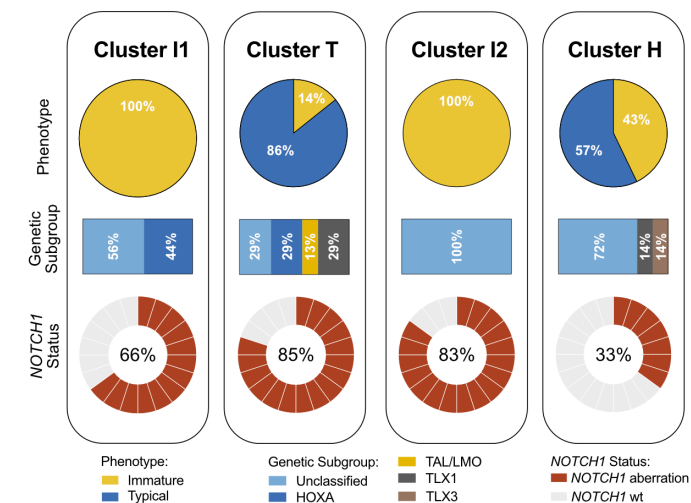
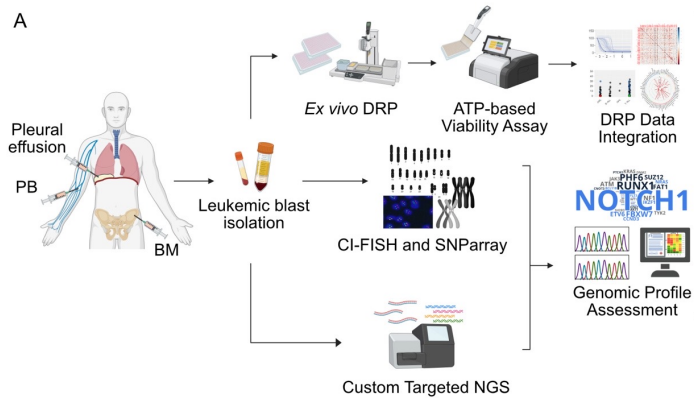
Can Functional Profiling Guide Treatment in R/R NHL?



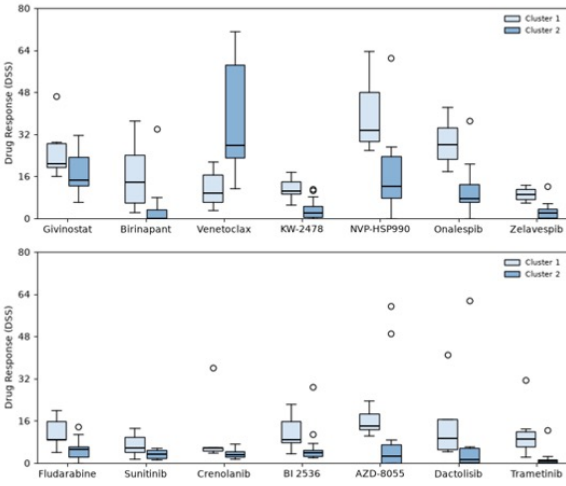
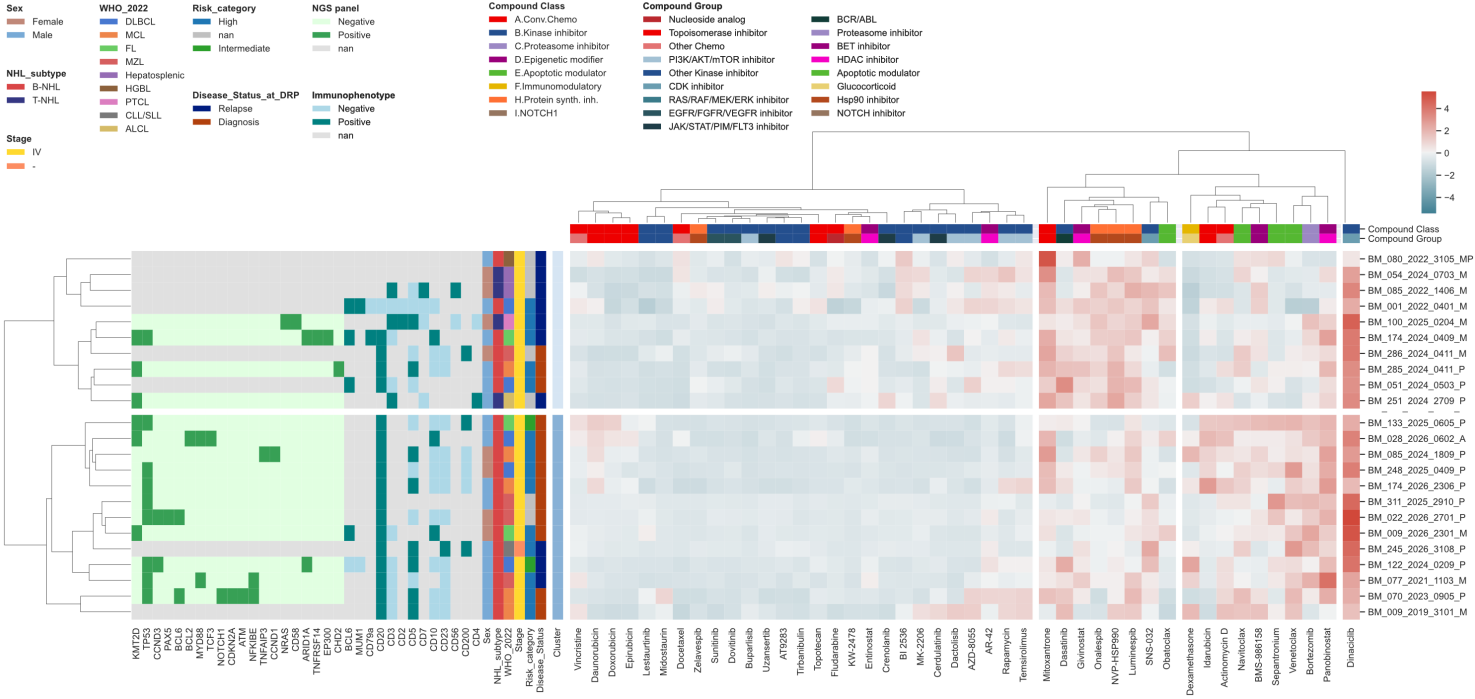
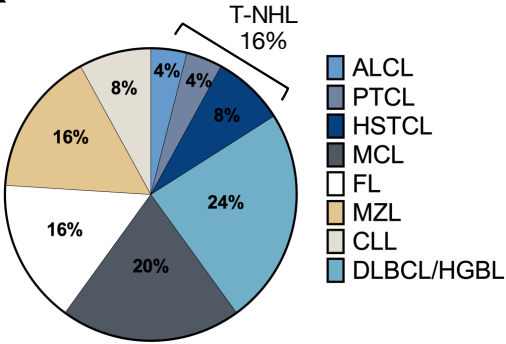
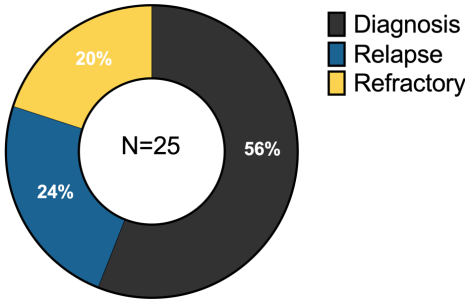
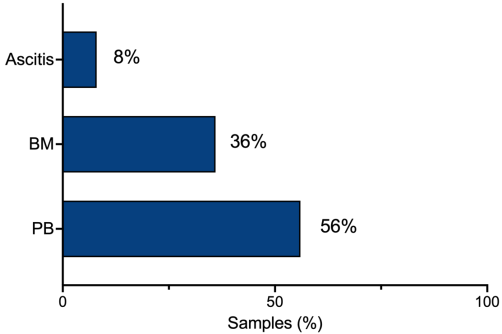
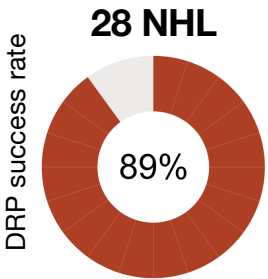
EXALT-1: Encouraging Data in Lymphoid Neoplasms



FPM in Italy: the GIMEMA ALL2720



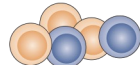
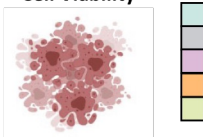
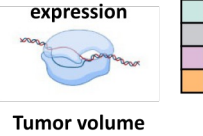
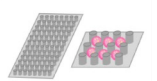
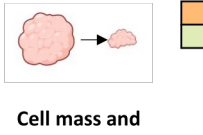
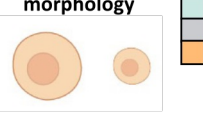
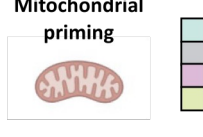
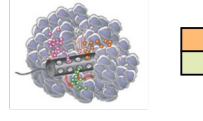
Ex vivo DRP in NHL @UNIPR



THEC data, unpublished

Challenges in Functional Multi-Omics

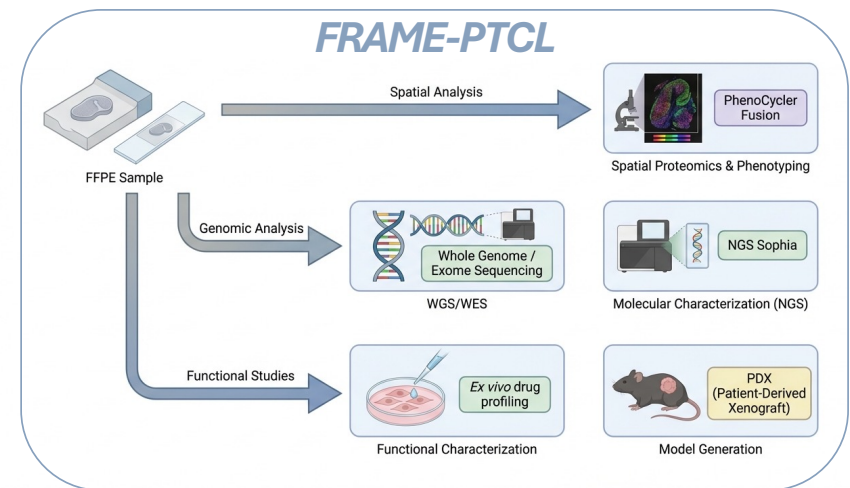
- Exponential technical variation
 - Batch effects
 - Incubation effects
 - Contaminations
- Microenvironment
- Appropriate model
- Missing value
 - Low cell counts
- Heterogeneous data type
 - Binary (e.g. mutations)
 - Continuous (e.g. drug response)
 - Counts (e.g. RNA-Seq)
- Complexity/Interpretability
 - E.g. Drug ranking score = drug response (per patient) - median drug response
- Clinical translation
 - Feasibility vs Predictive value vs Clinical utility

Patient derived model	Advantage	Disadvantages	Readouts to assess drug response
2D culture 	- Rapid expansion - Low cost - High throughput - Amenable to rapid testing	- Prolonged ex vivo culture; assay dependent - Missing many microenvironment components - Non-physiologic culture conditions	Cell Viability 
3D Organoids 	- Mimics the 3D tumor environment - Moderate cost - Moderate throughput - Amenable to rapid testing; assay dependent	- Prolonged ex vivo culture; assay dependent - Missing some microenvironment components - Non-physiologic culture conditions	Gene/protein expression 
Microfluidics & Engineered Microenvironments 	- Engineered tumor microenvironment - Amenable to rapid testing; assay dependent	- Prolonged ex vivo culture; assay dependent - Missing some microenvironment components - Generally low throughput	Tumor volume 
Patient Derived Xenografts 	- in vivo tumor environment - Incorporates drug pharmacokinetics - Clear toxicity readout	- Slow expansion - High cost - Low scalability - Tumor-host species differences - Lacking immune system	Cell mass and morphology 
Human Patient 	- Human microenvironment - Avoids model establishment	- Regulatory barriers - Biopsies required to rapidly assess response	Mitochondrial priming 
			Implantable microdevice 

Adapted from Cancer Cell, 2022; (40)26:31

Conclusions

- Functional ex vivo drug profiling and chemogenomic screens can facilitate:
 - Identification of actionable targets at the single-patient level
 - Identification of molecular drivers at the population level
- Reverse this information to identify new disease biomarkers
- Functional profiling should be included in a multi-layer lymphoma characterization to provide novel disease biomarkers and vulnerabilities.



- In lymphoma, results depend on the sampled cells and the biological context reproduced by the model.
- Potential clinical application for relevant drug-repositioning opportunities, bridge-to-CAR-T/HSCT, and novel N-of-1 FPM trials.

Acknowledgements

University Hospital of Parma, FPM Unit

Prof. Giovanni Roti, MD, PhD

Mariateresa Giaimo, MD, PhD

Roberto Rosati, PhD

Raffaella Zamponi, BS

Benedetta Cambò, MD, PhD

Alessia Ballarò

THEC lab

Anna Montanaro, PhD

Andrea Gherli, BS

Federica Vento, PhD

Elisa Simoncini, PhD

Luciano Nicosia, PhD

Davide Carnevali, PhD

Gregorio Monica, PhD student

Marika Malchionna, PhD student

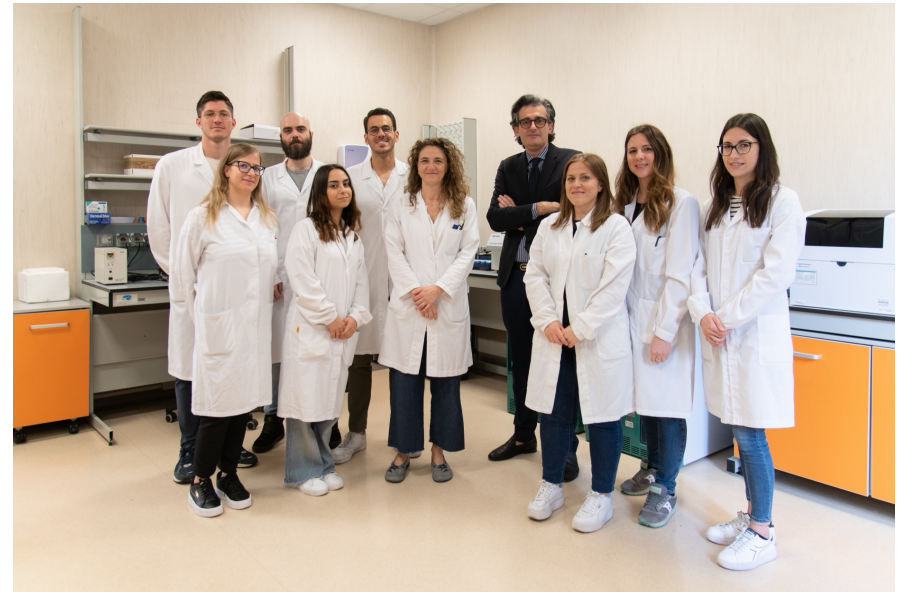
Sabrina Testa, MD, PhD student

Lymphoma Unit, Parma

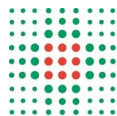
Caterina Plenteda, MD

Maria Ilaria Nasuto, MD

Filomena Russo, MD



fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica
sulle malattie ematologiche. **FRANCO MANDELLI**



**SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA**
Azienda Ospedaliero - Universitaria di Parma



Finanziato
dall'Unione europea
NextGenerationEU



Ministero
dell'Università
e della Ricerca



Italiadomani
Piano Nazionale
di Ripresa e Resilienza



ICGC
International Cancer
Genome Consortium

Spoke 8
In Silico Medicine & Omics Data



luca.pagliaro@unipr.it
thec.drp@gmail.com

