Weill Cornell Medicine
Sandra and Edward
Meyer Cancer Center

Weill Cornell
Medicine

Lymphoma Conference

Giorgio Inghirami
Department of Pathology and Laboratory Medicine
Weill Cornell Medicine, New York, NY

Rome,
March 16-17, 2023

Donna Camilla Savelli Hotel

President: P.L. Zinzani

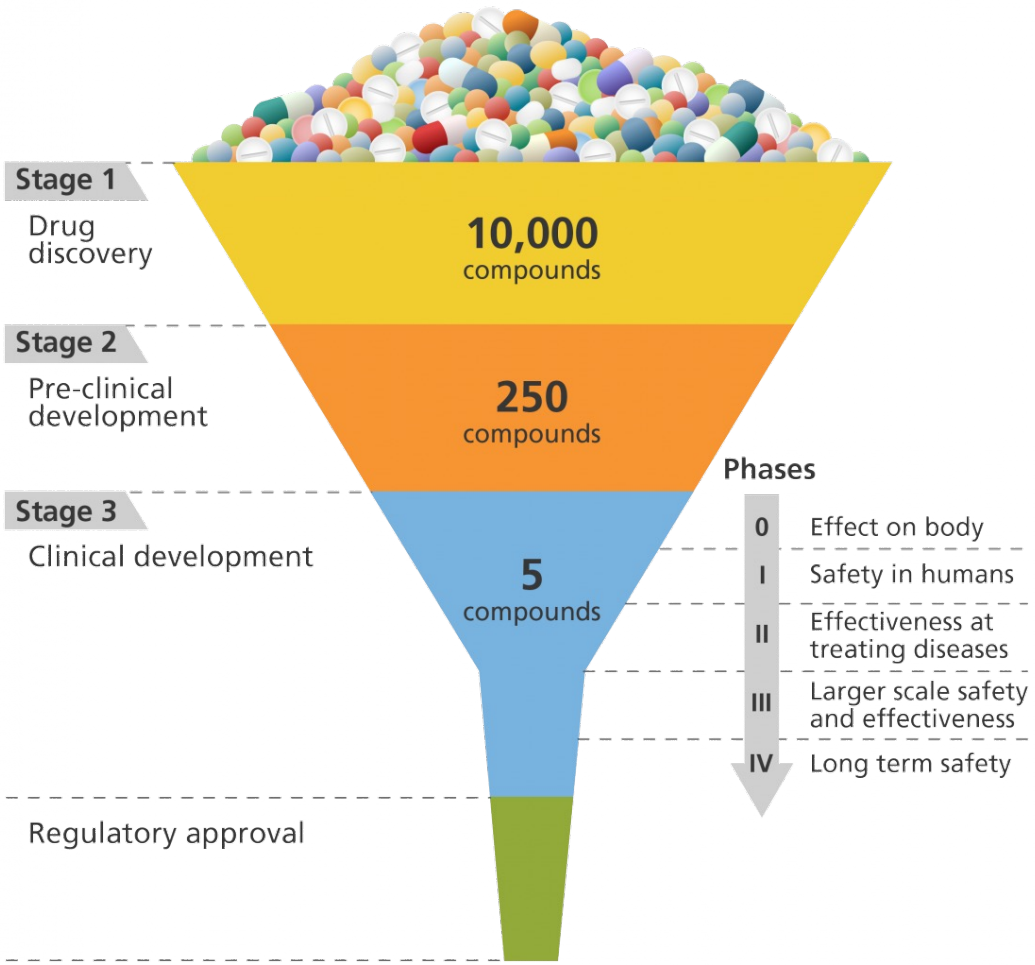
Weill Cornell Medicine
Sandra and Edward
Meyer Cancer Center

Weill Cornell
Medicine

Conflict of interest declaration

Financial support to Weill Cornell Medicine: Kymera Therapeutics, Inc

Why we need pre-clinical platforms in oncology?



1 compound

Weill Cornell Medicine

SCIENTIFIC AMERICAN™

Sign In | Register 0

Search ScientificAmerican.com

Subscribe | News & Features | Topics | Blogs | Videos & Podcasts | Education | Citizen Scienc

Health » Chemical & Engineering News

5 :: Email :: Print

Cost to Develop New Pharmaceutical Drug Now Exceeds $2.5B

A benchmark report estimates that the cost of bringing a drug to market has more than doubled in the past 10 years

The article also includes estimates of the costs to develop each drug. The $6 billion tab for Sanofi and Regeneron Pharmaceuticals' eczema drug Dupixent is an outlier, and researchers ranked the quality of their evidence support that estimate as "low."

But several drugs emerging from the Sanofi-Regeneron collaboration also had high estimates. Those include Praluent at more than $3 billion each, along with Kevzara, Zaltrap and Libtayo at more than $2 billion each. Regeneron's wholly owned Eylea also was estimated to have cost more than $3 billion.

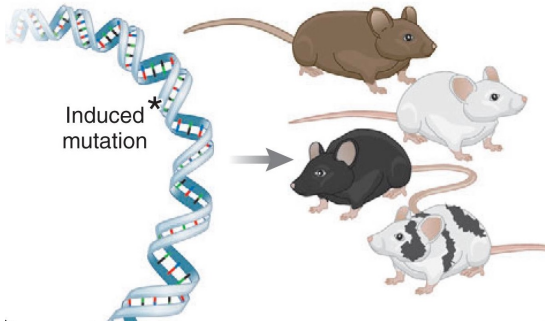
Drug development 6.7 yrs | ***FDA approval*** 10.1 months | ***Clinical testing*** 8 yrs

Time

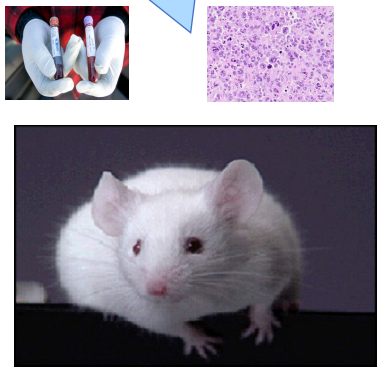
Weill Cornell pre-clinical discovery platforms and PATh Core

Zebra Fish Transgenes

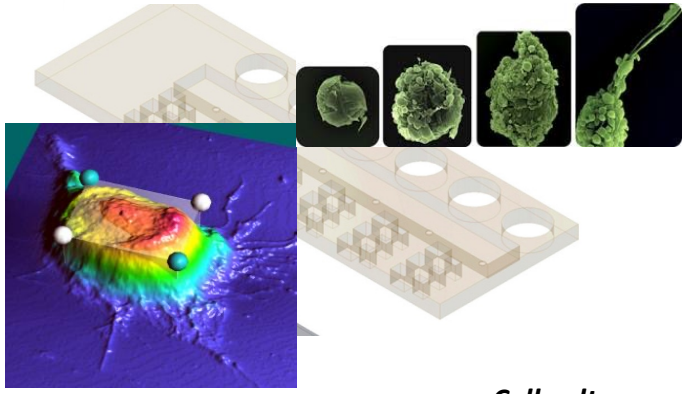
Genetically engineered mice (GEM)

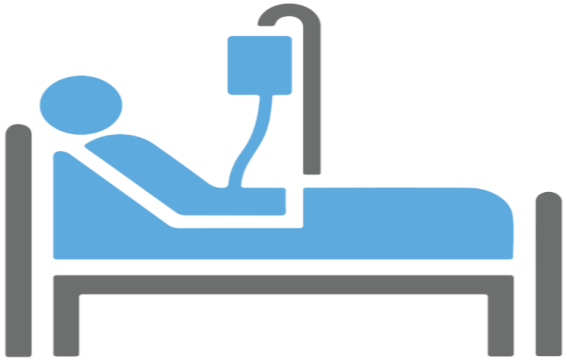


Patient Derived Tumor Xenografts (PDTX)

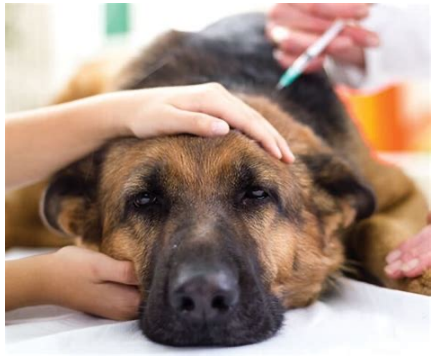


Micro-organoids

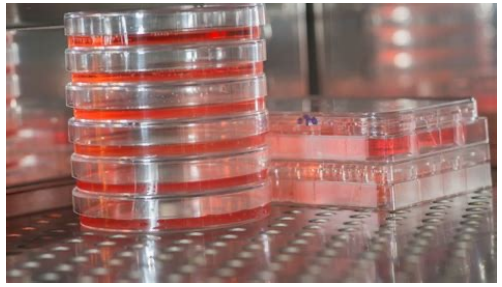




Drug discovery-Immuno-therapies-vaccines

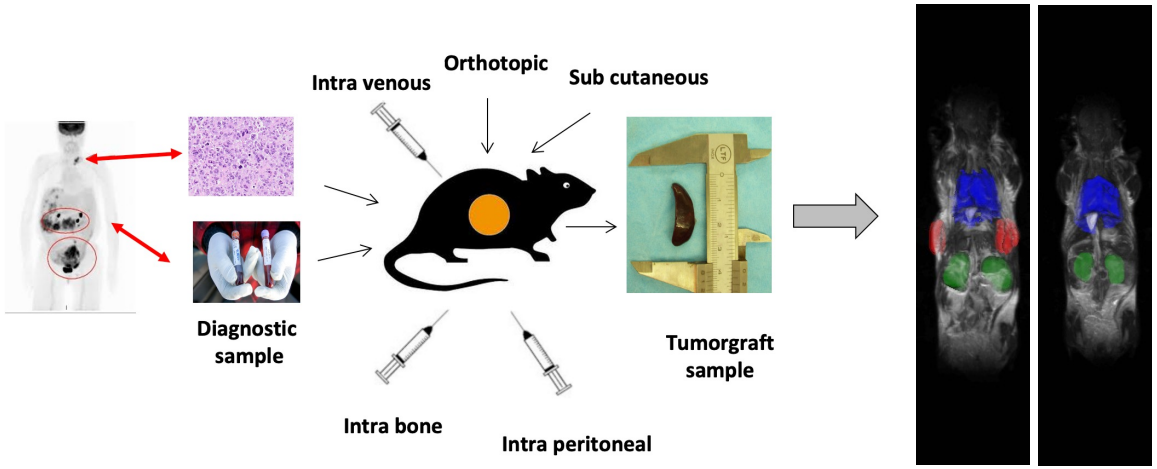


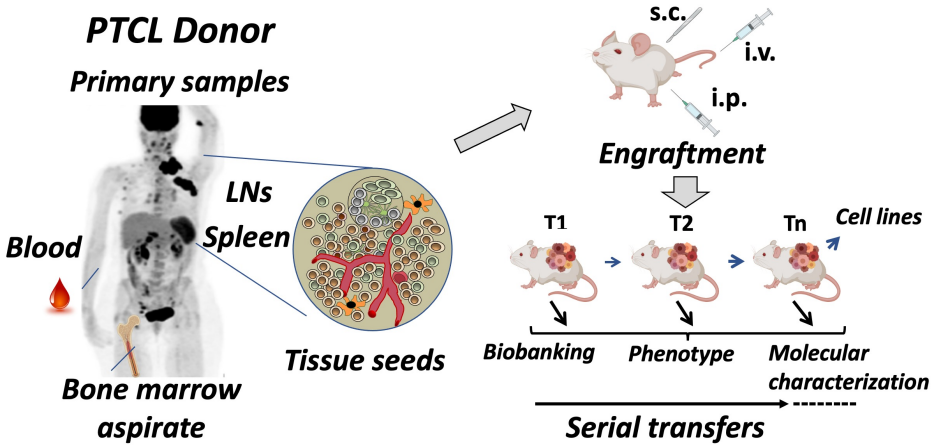
Cell cultures

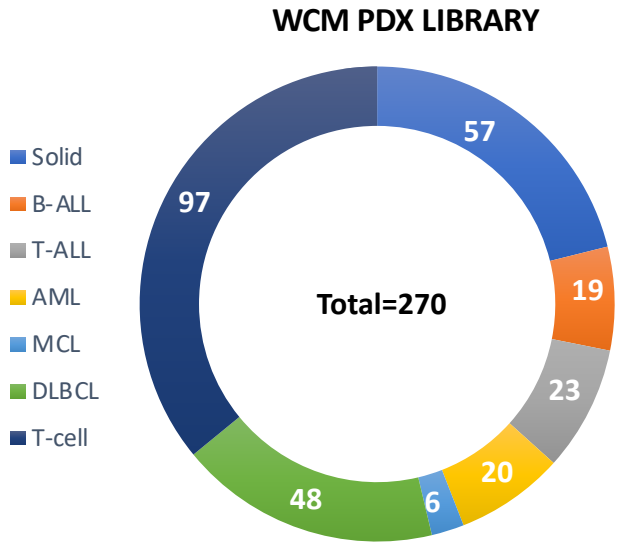


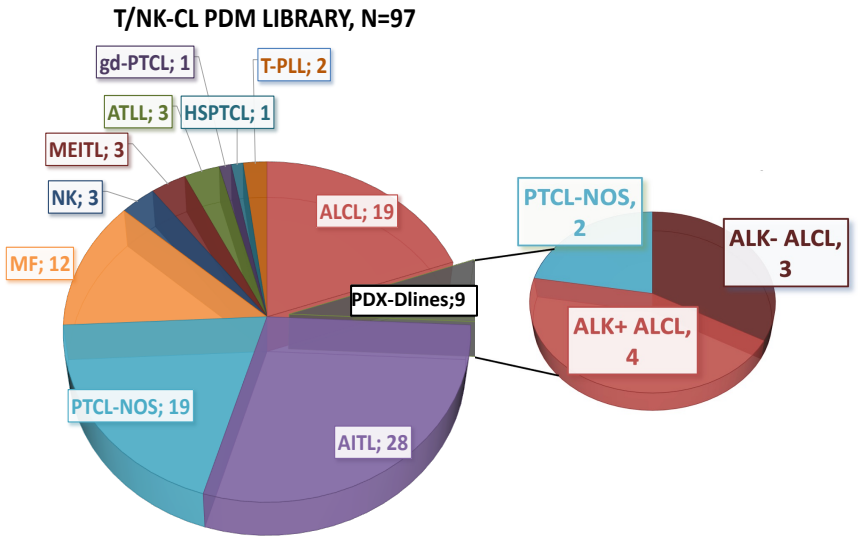
WCMC -Cornell Ithaca

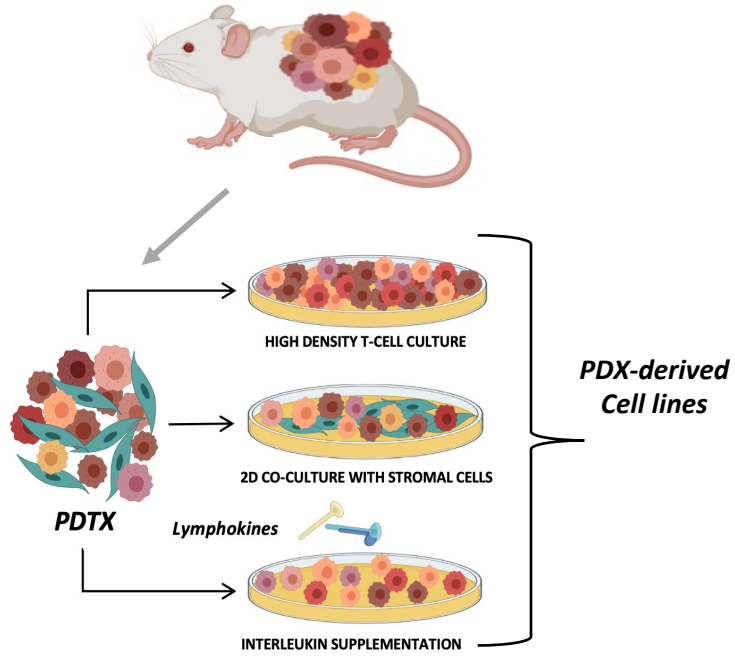
PDX and The Pre-clinical Models



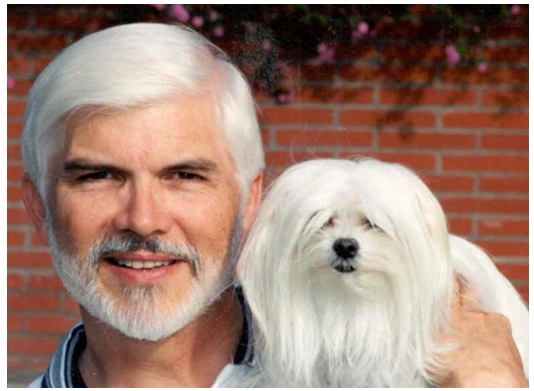




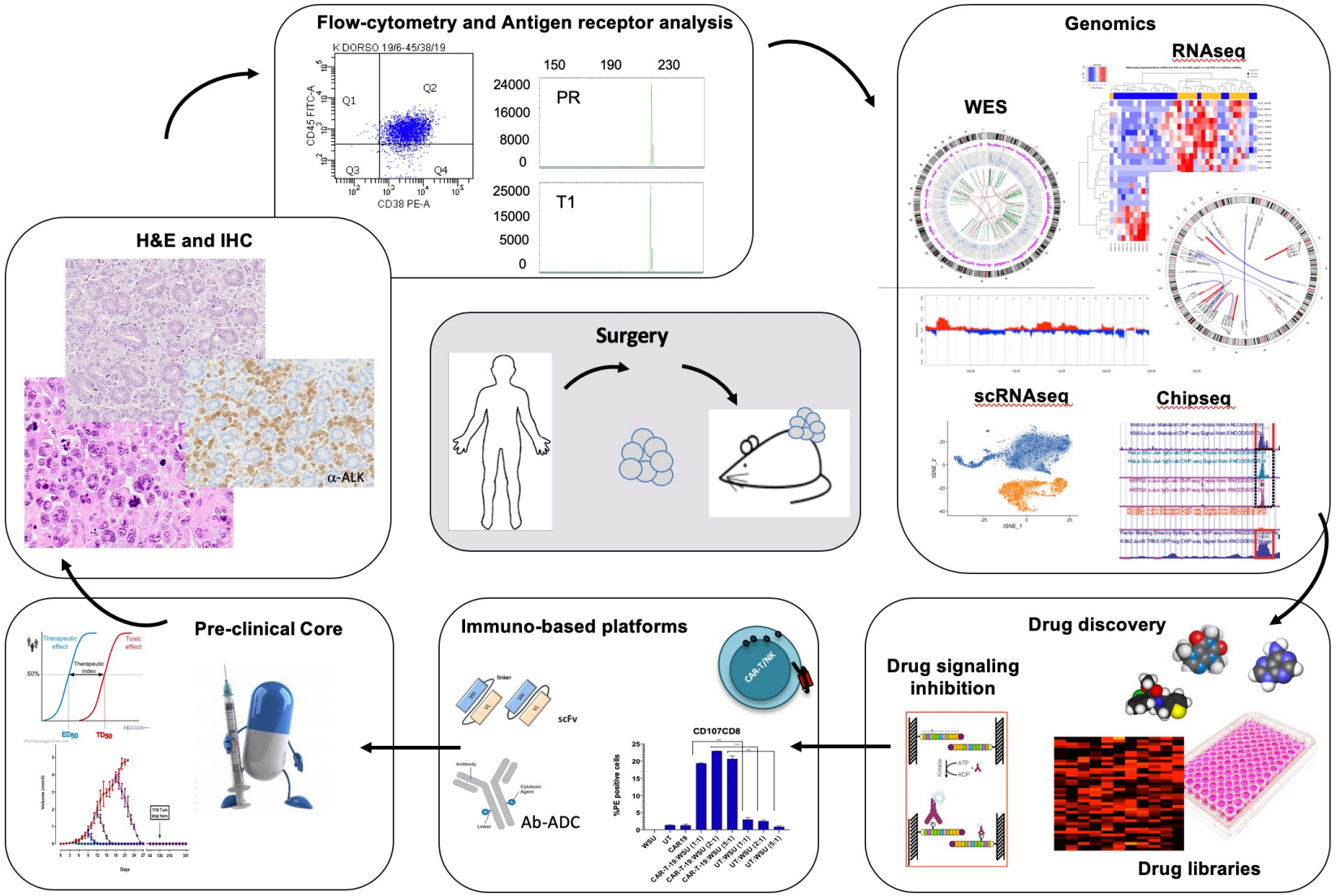




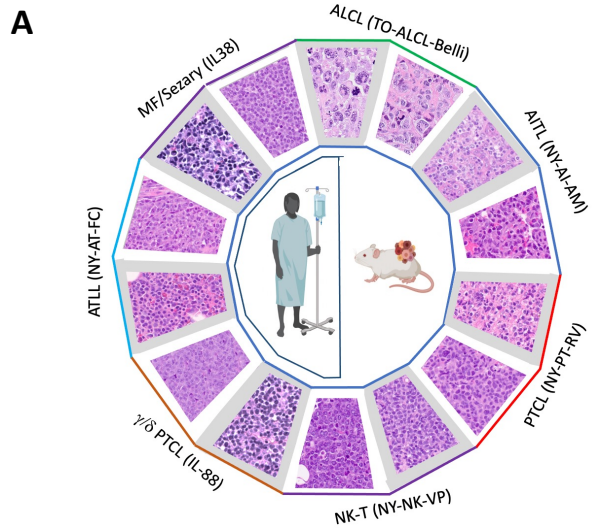
PDX closely mimic primary tumors but.....

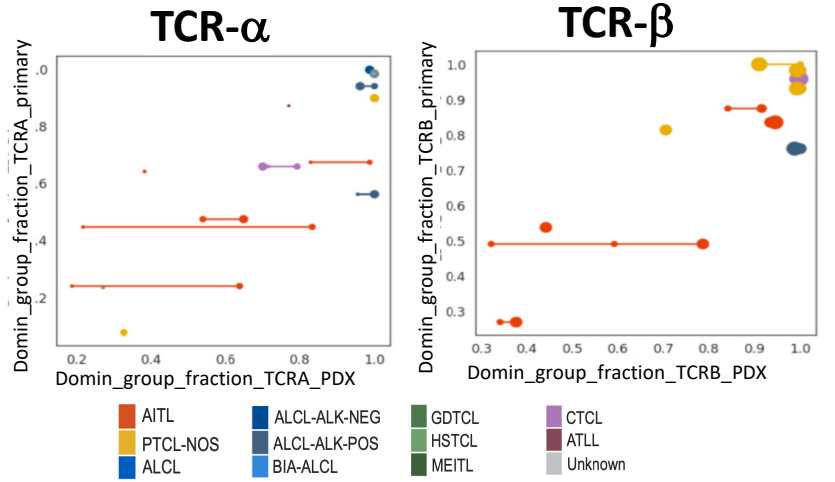


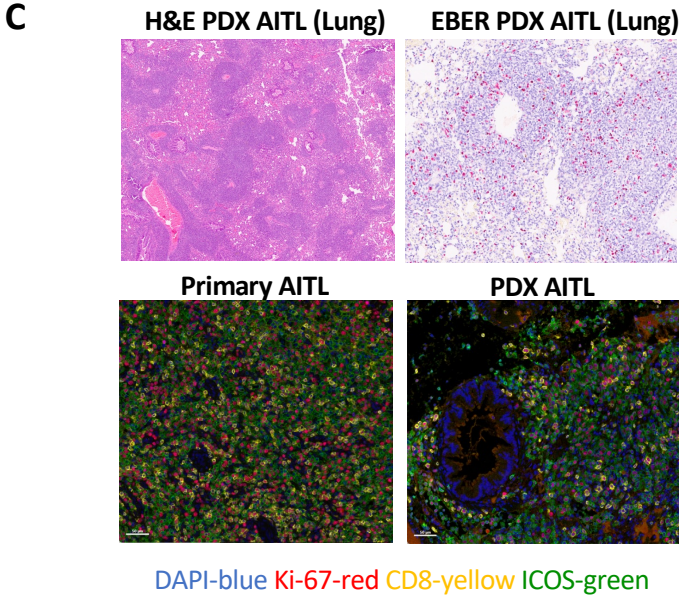
Molecular and functional platforms to characterize and stratify PDTX

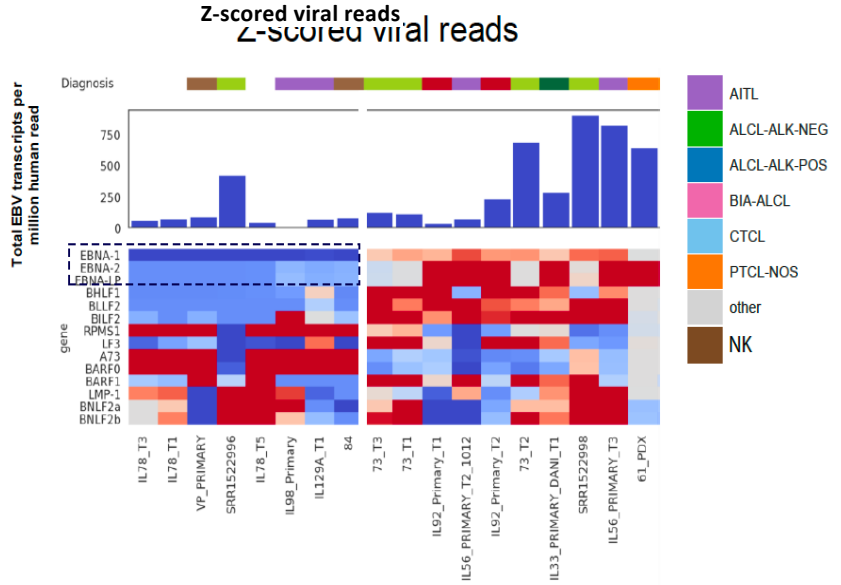


Phenotypic and molecular characterization of PTCL PDTX



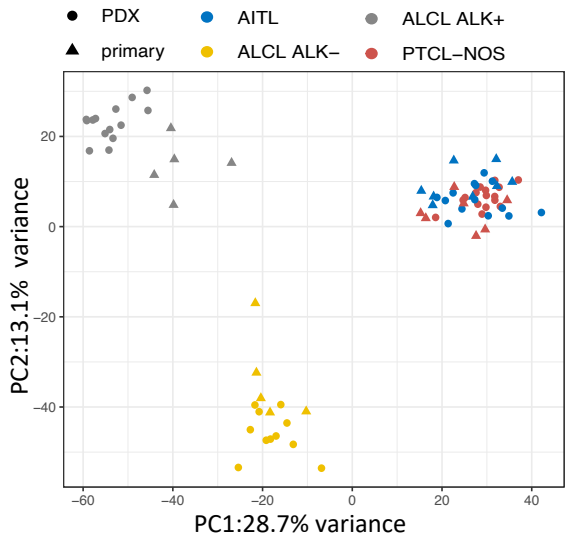




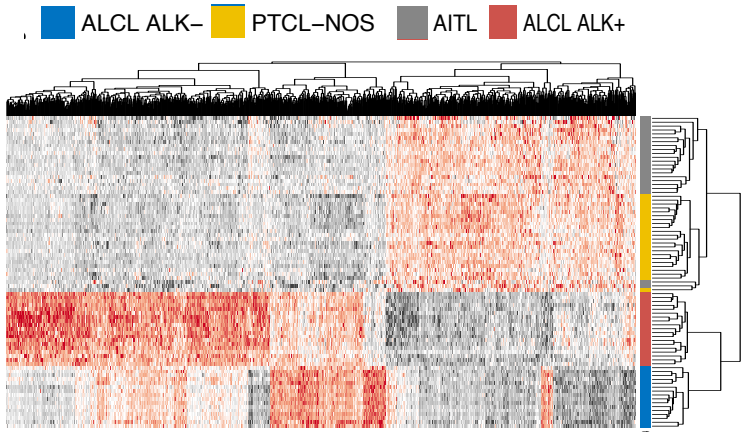


Transcriptomic profiles of PTCL PDTX mimic primary lesions and identify novel genomic aberrations

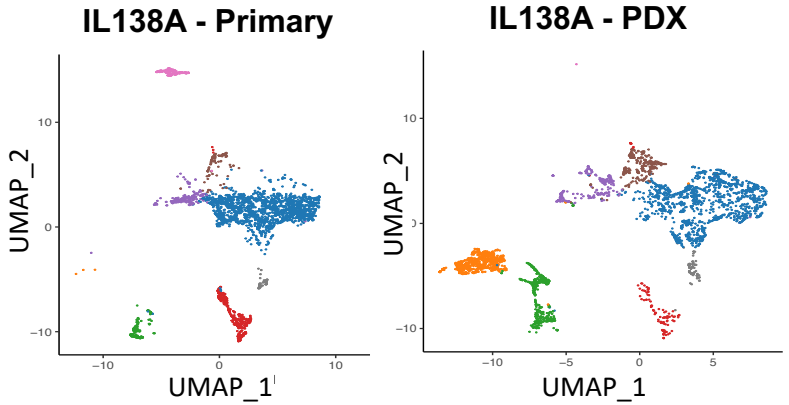
A



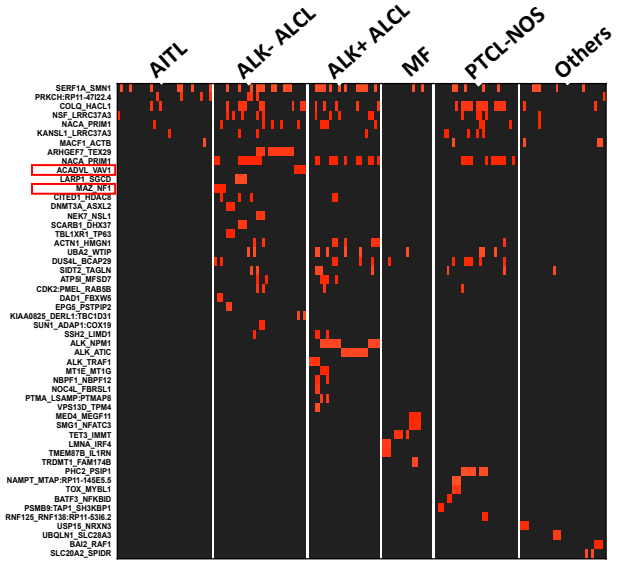
B



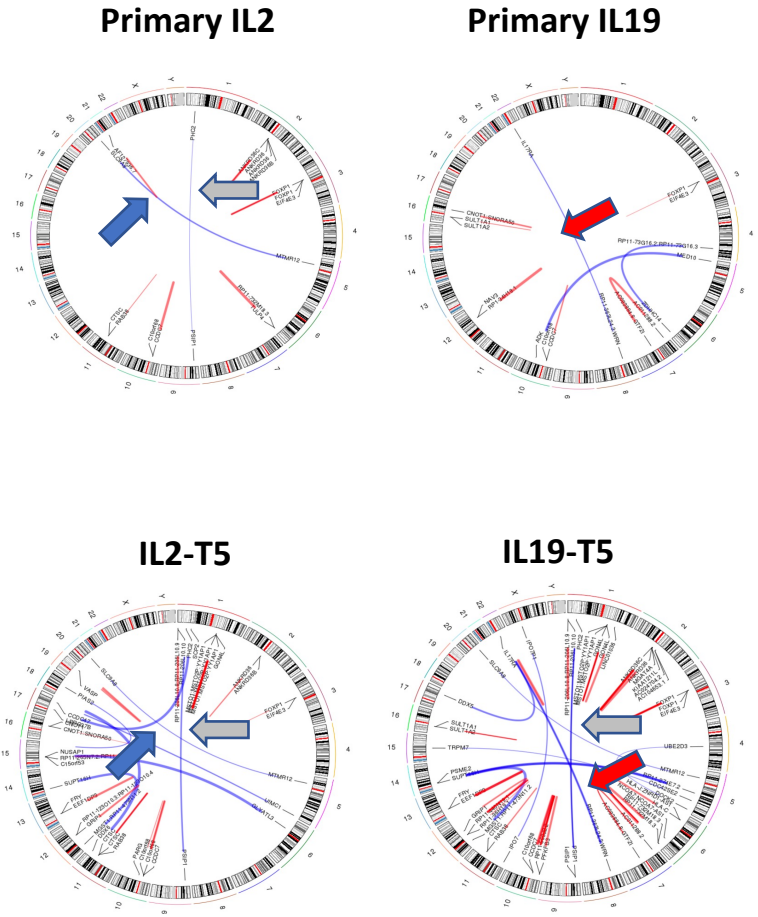
C



D

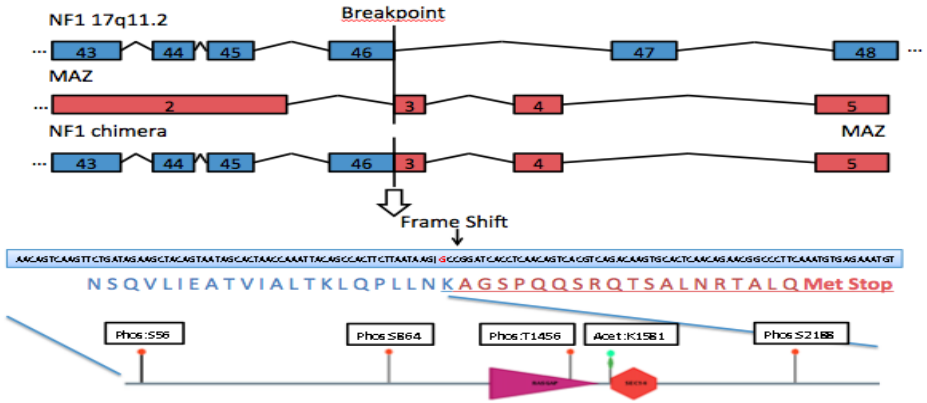


E

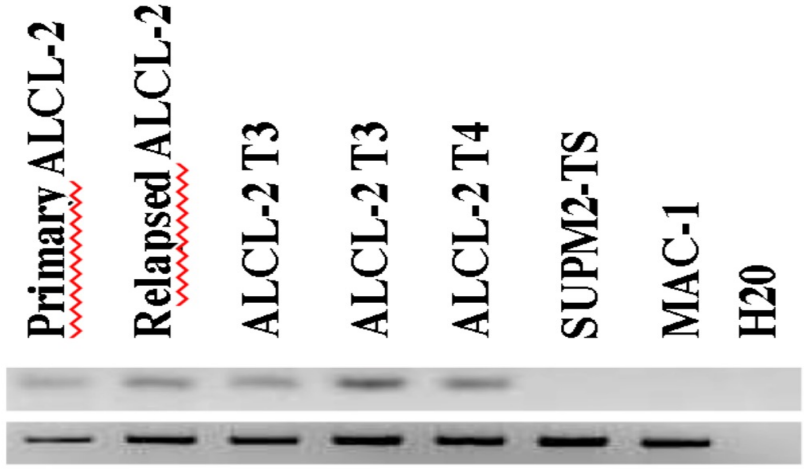


PDX transcriptional profile define novel vulnerabilities of PTCL: NFA1-MAZ fusion

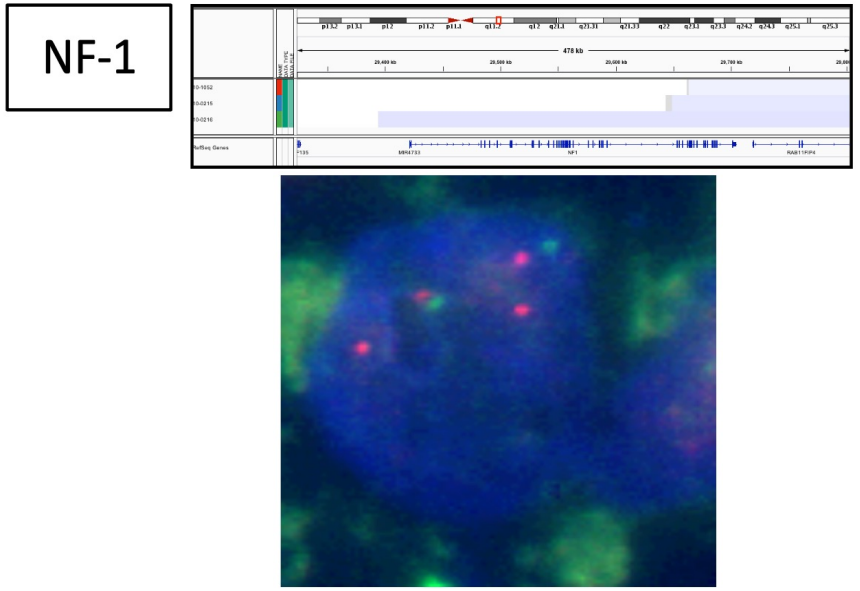
A



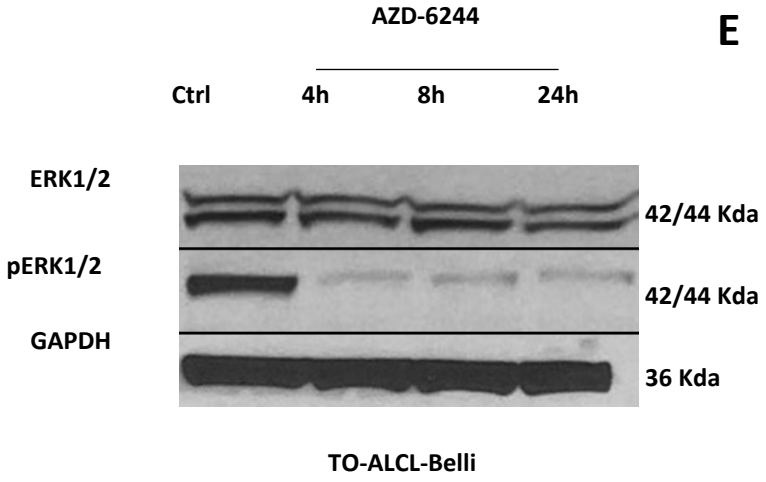
B



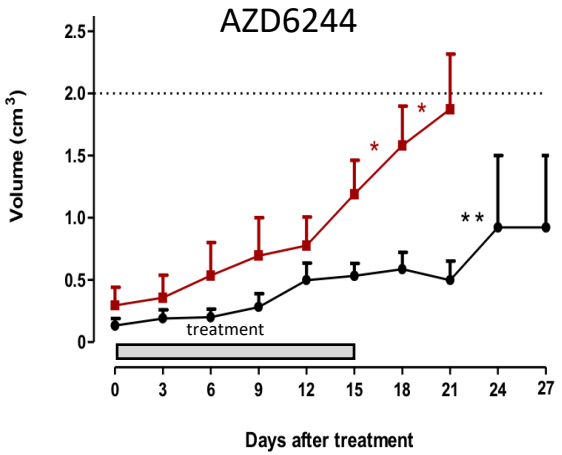
C



D

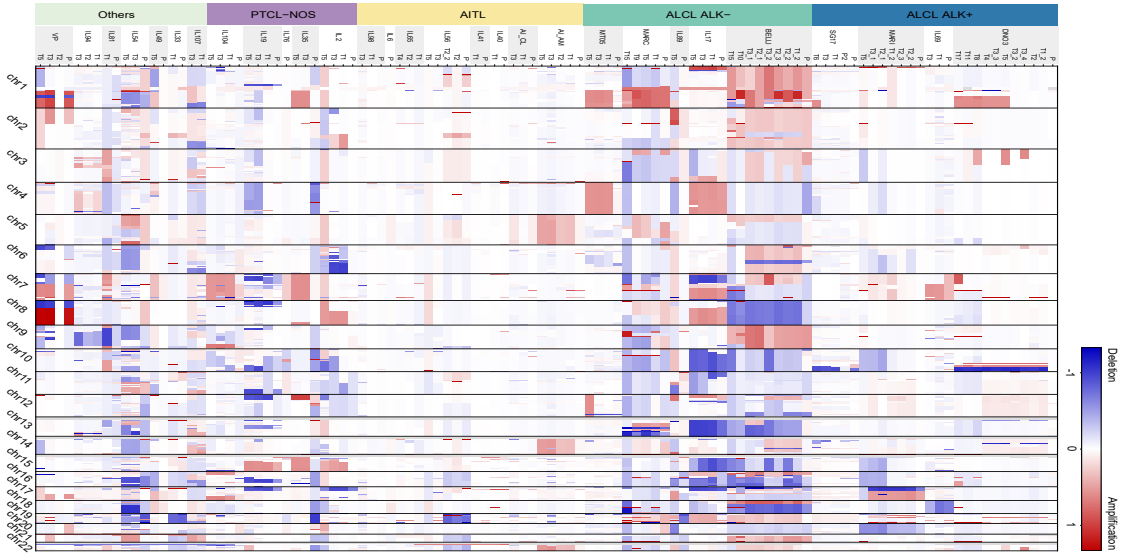


E

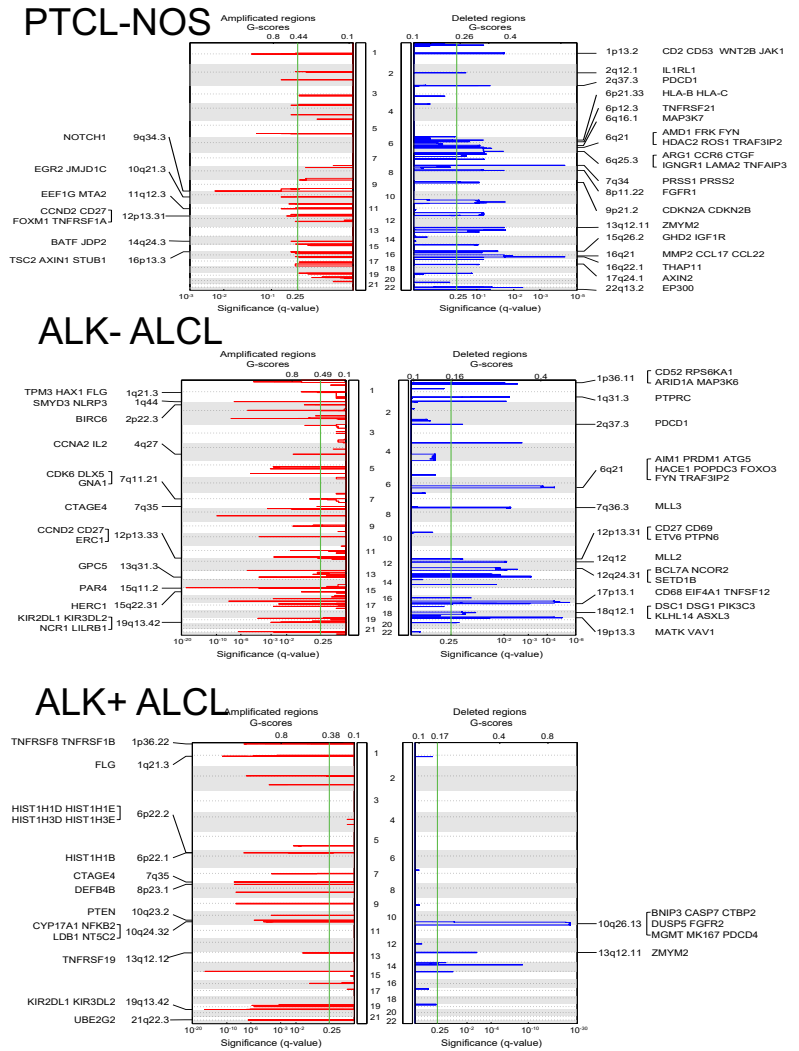


Molecular stratification of PDX provide the basis for patients' stratification and cancer evolution

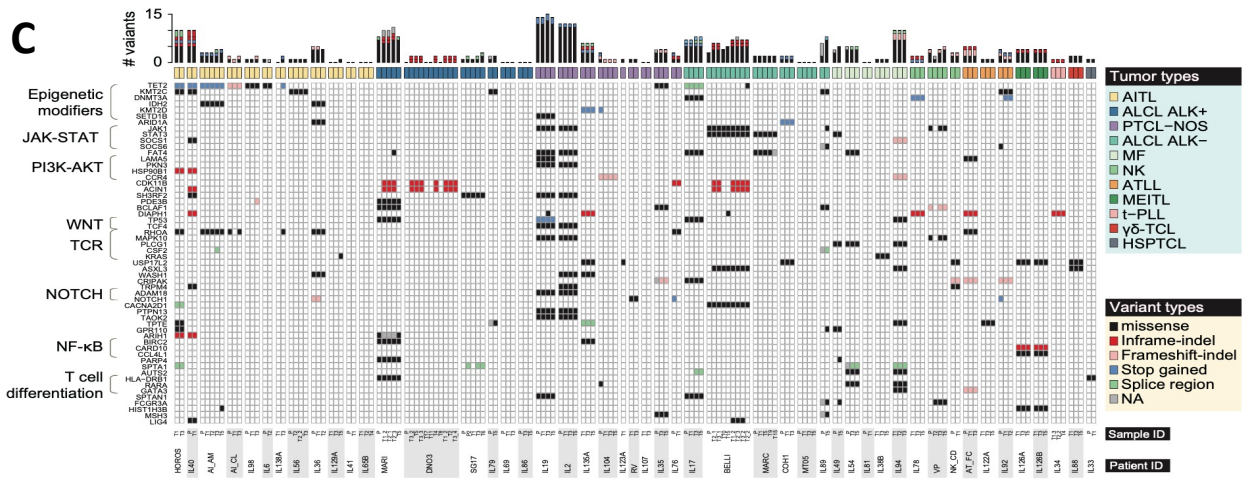
A



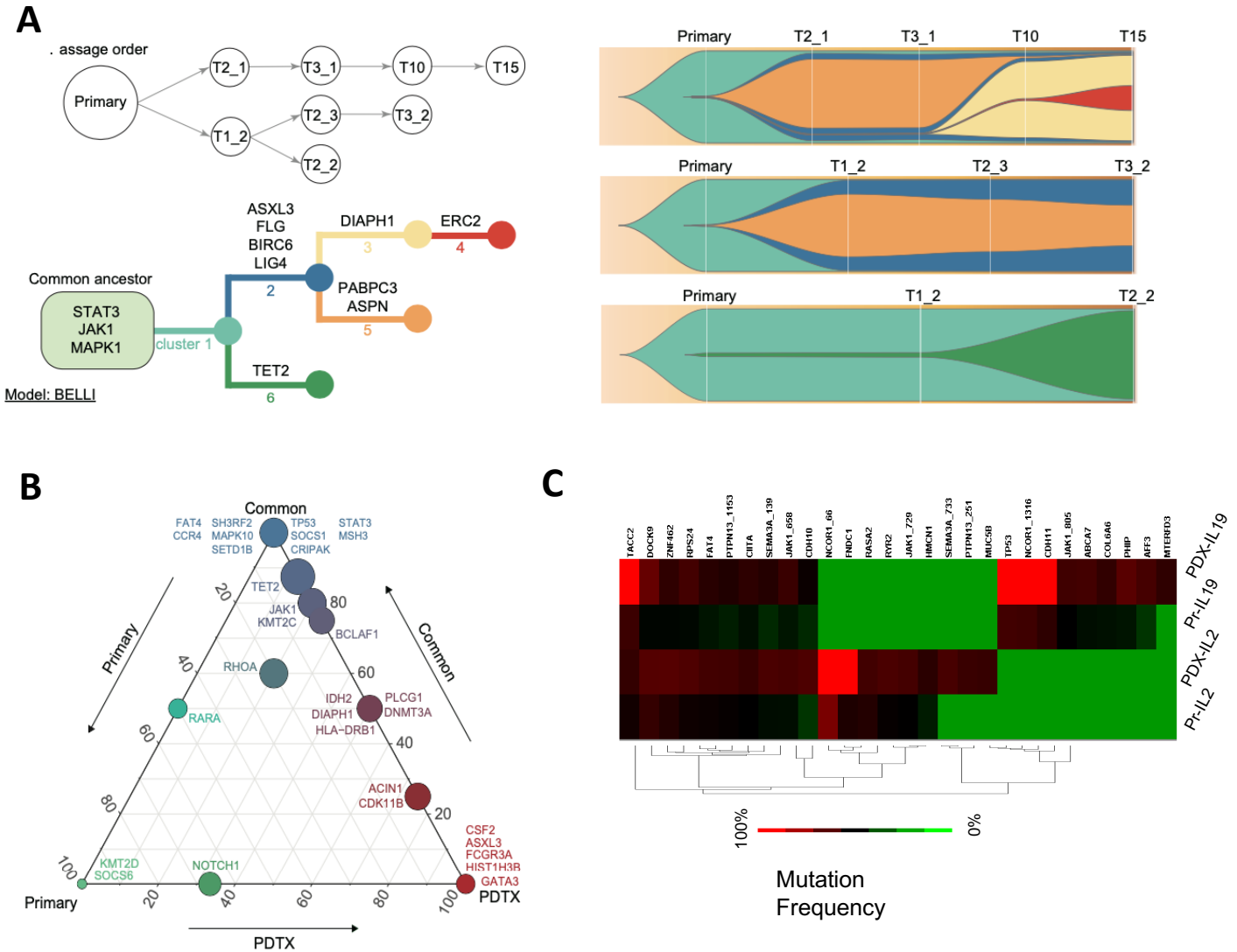
B



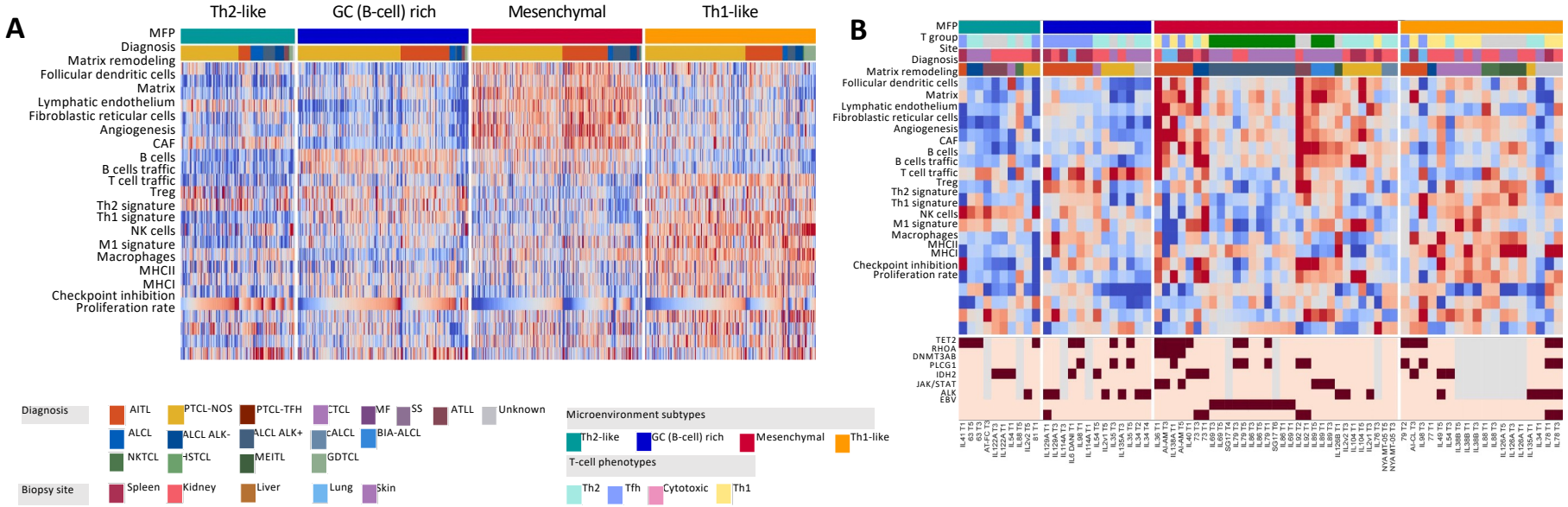
C

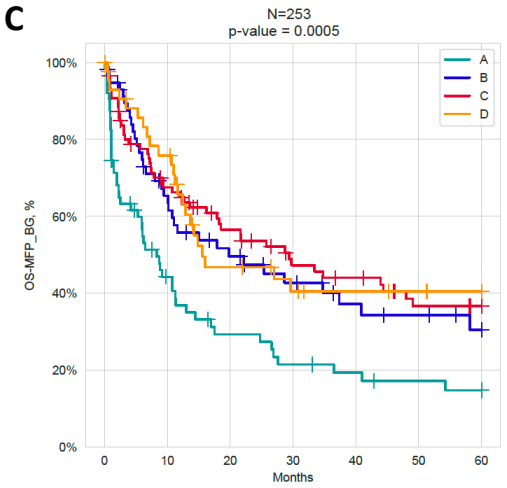


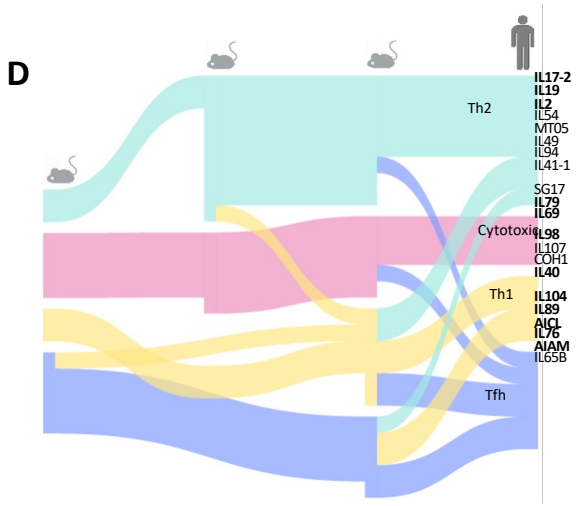
Molecular stratification of PDX provide the basis for patients' stratification and cancer evolution



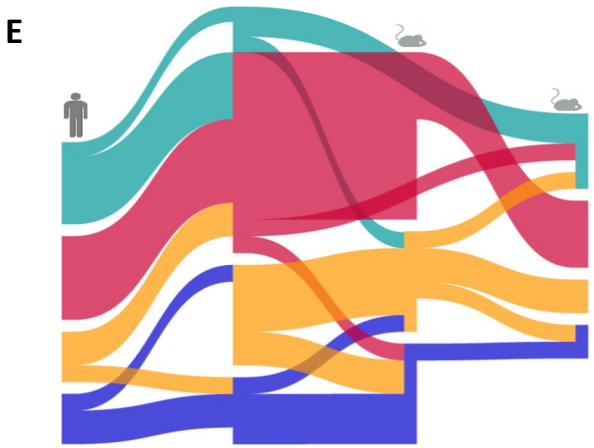
Host-driven stratifications define distinct subgroups of PDTX





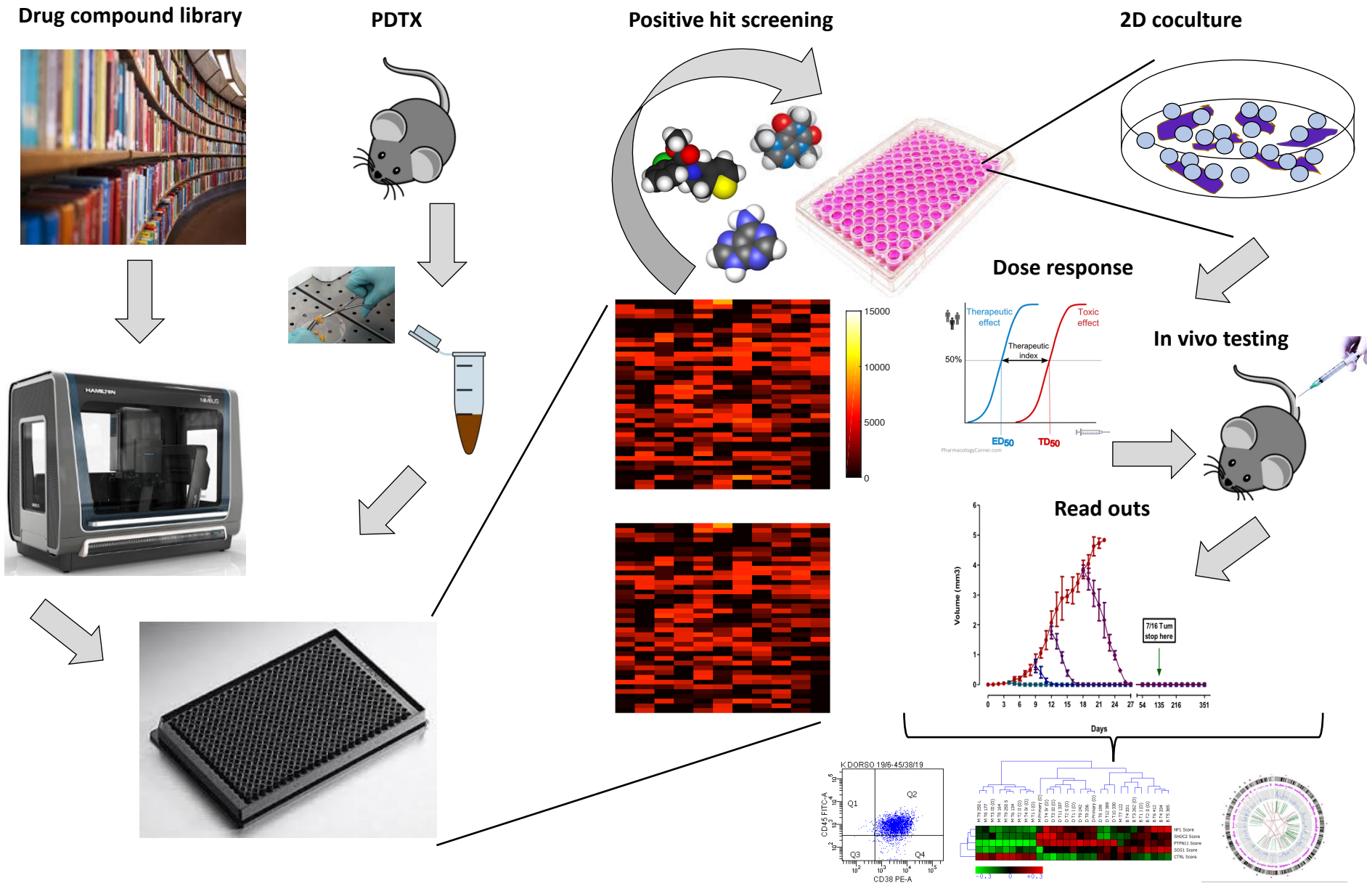


Intrinsic pathway
(T cell phenotypes)

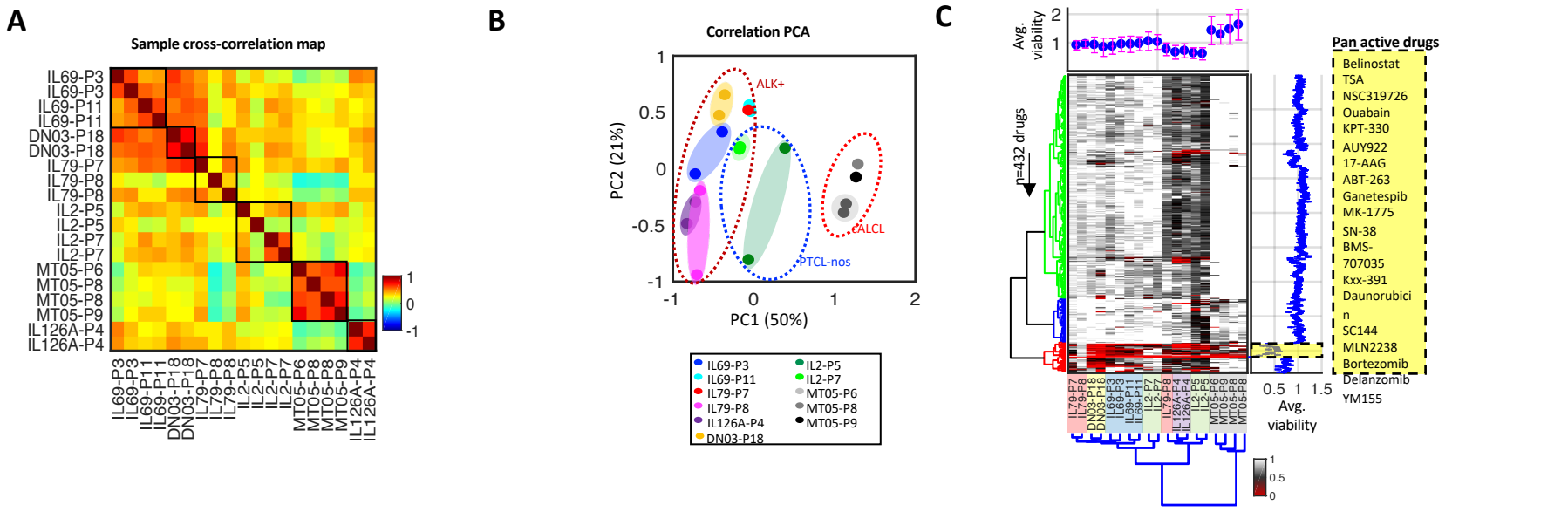


Extrinsic pathway
(PTCL microenvironment subtypes)

Drug screening platform with PDTX libraries

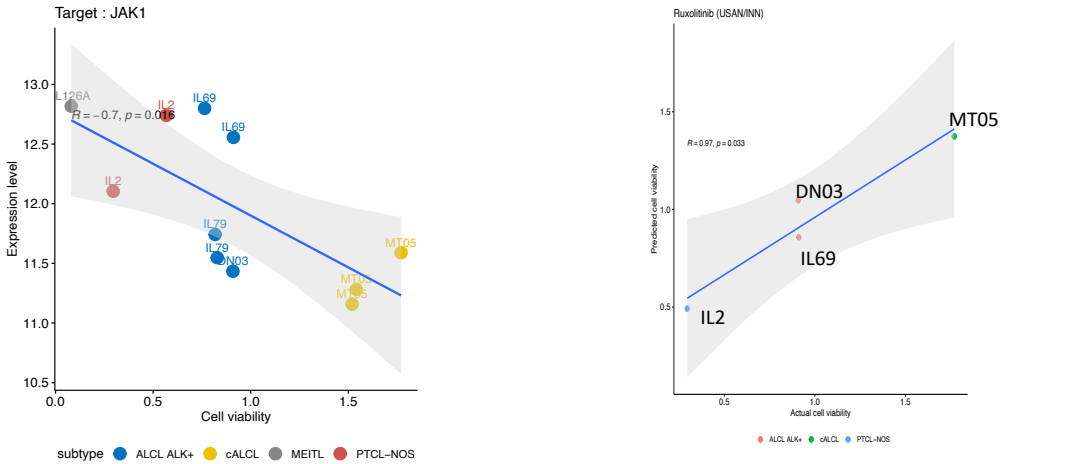


Drug screening platforms with PDTX libraries

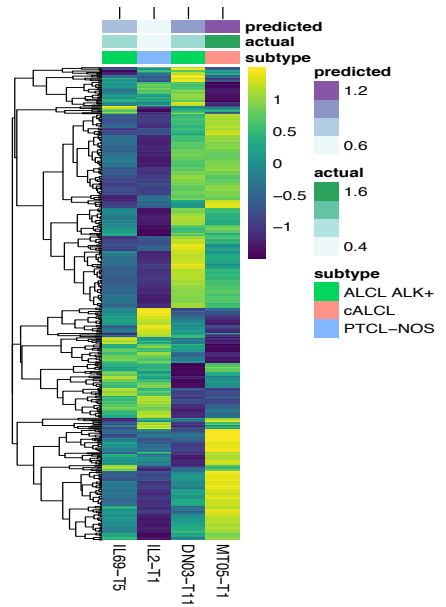


D

Ruxolitinib

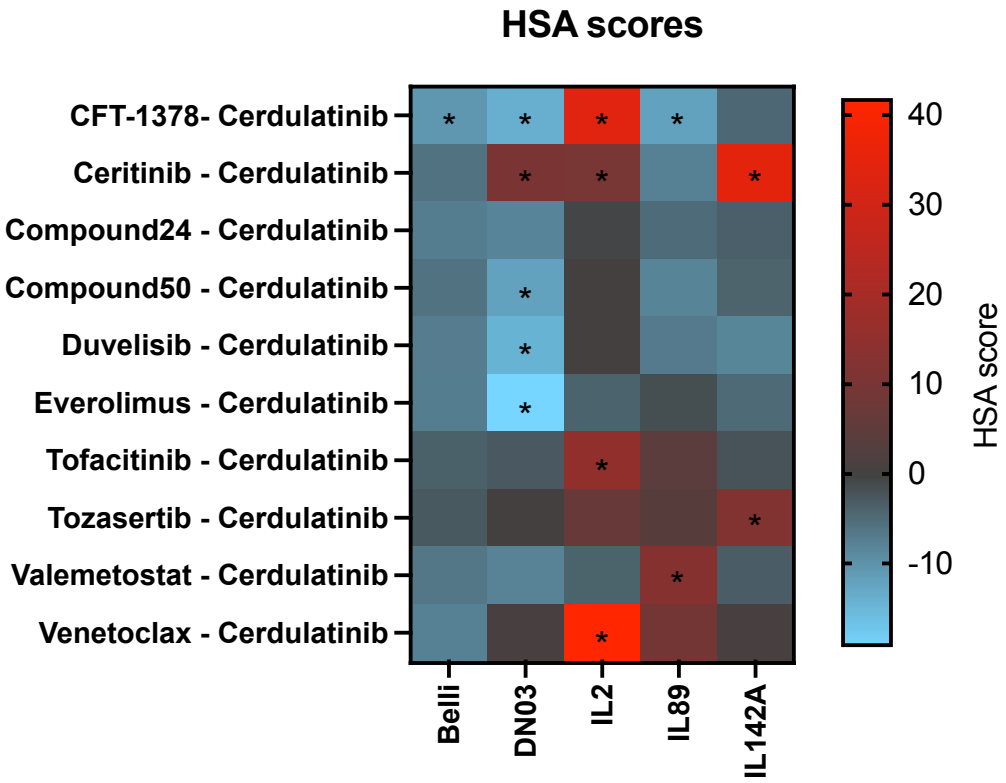


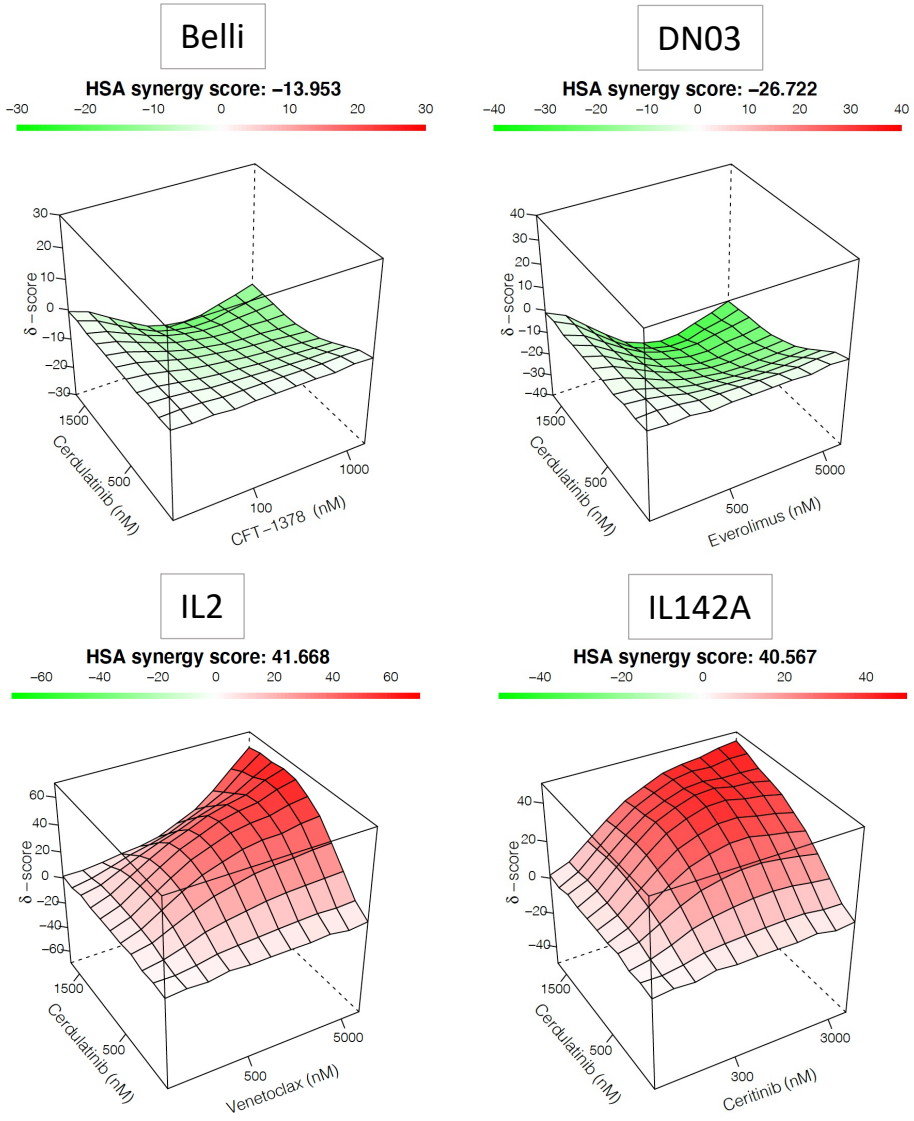
E



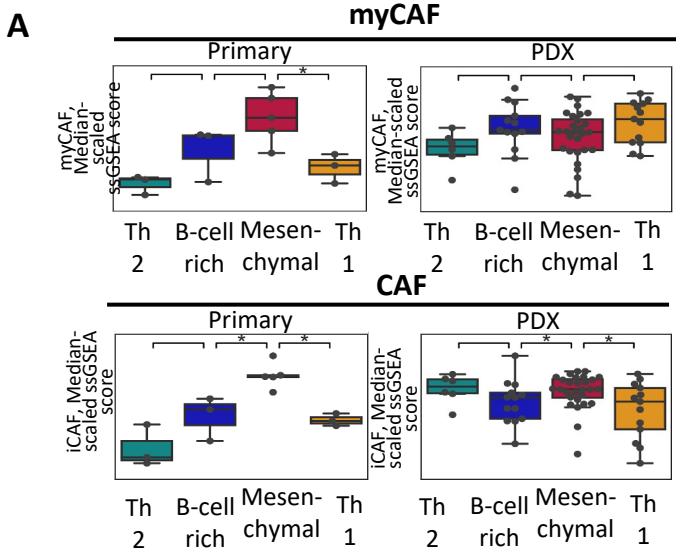
Mathematical program to assess drug synergies in PDX treated cells

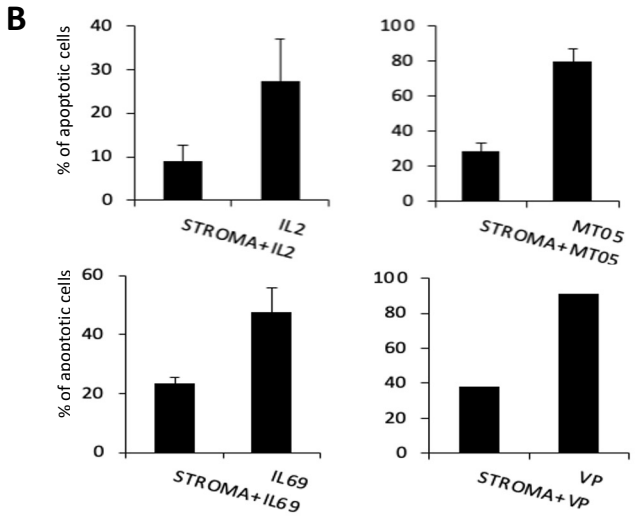
Cerdulatinib synergy screening

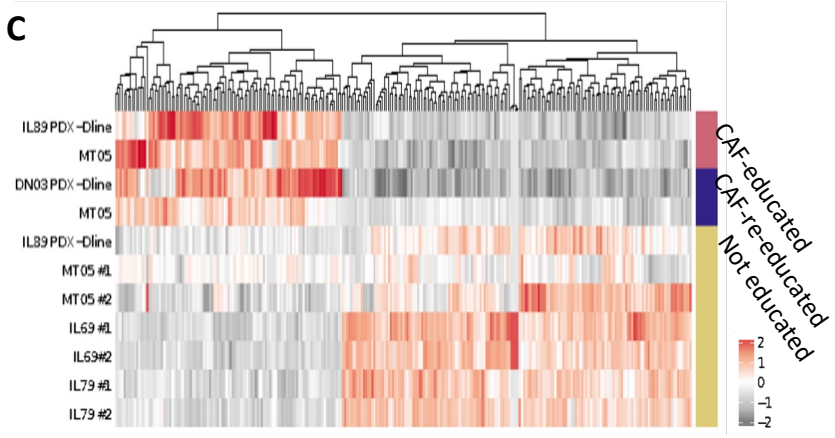


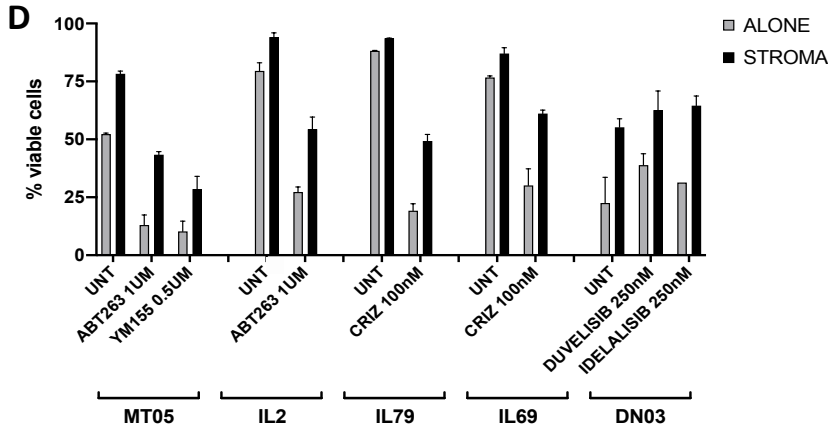


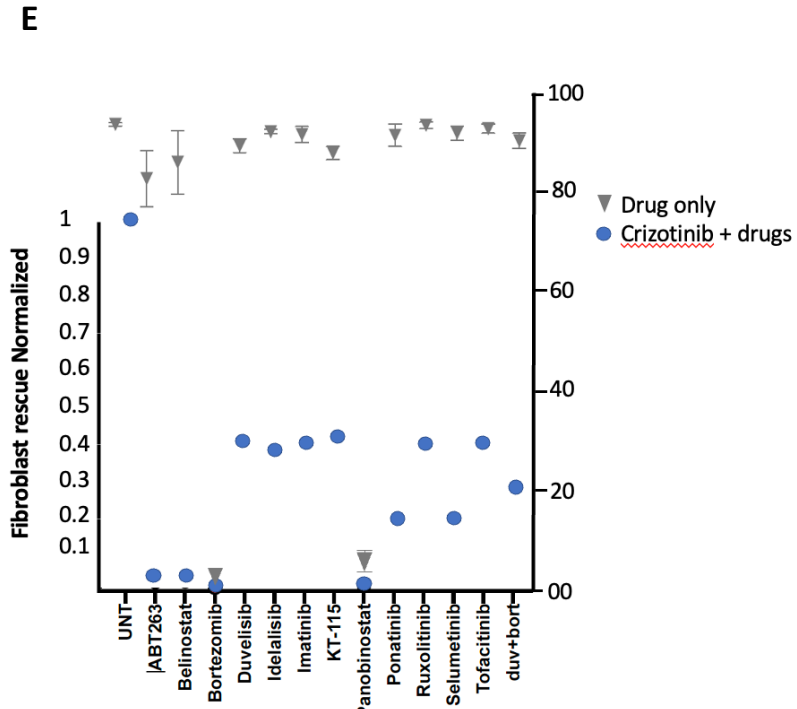
Stromal elements modulate the survival and drug responses of PDX PTCL









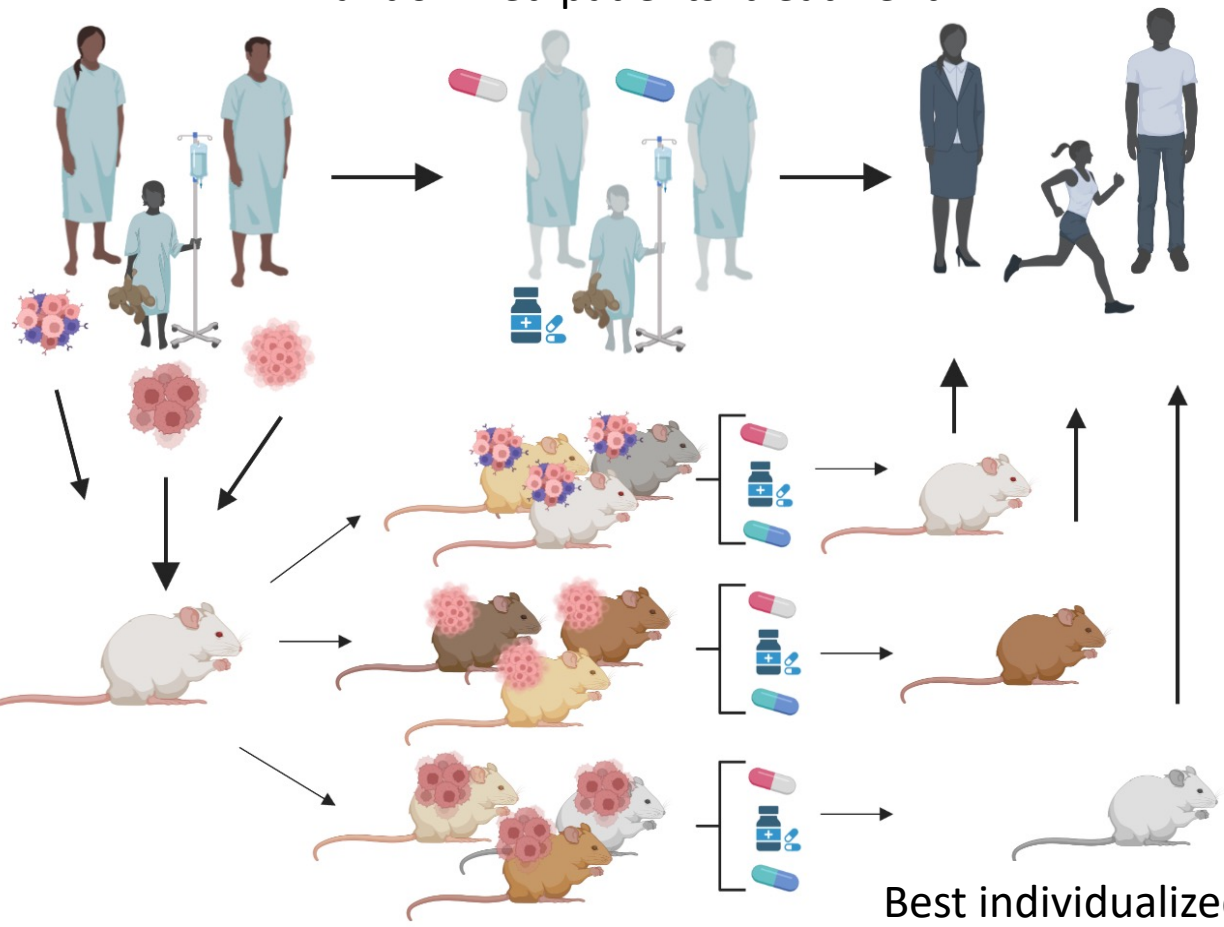


Matched co-clinical mouse-human trials

The co-clinical paradigm aims to develop mouse trials in parallel with human clinical trials to enable rapid, real-time transfer optimization and outcomes improvement to individual patient.

off

Randomized patients' treatment



Optimized therapies
→
Improved outcomes

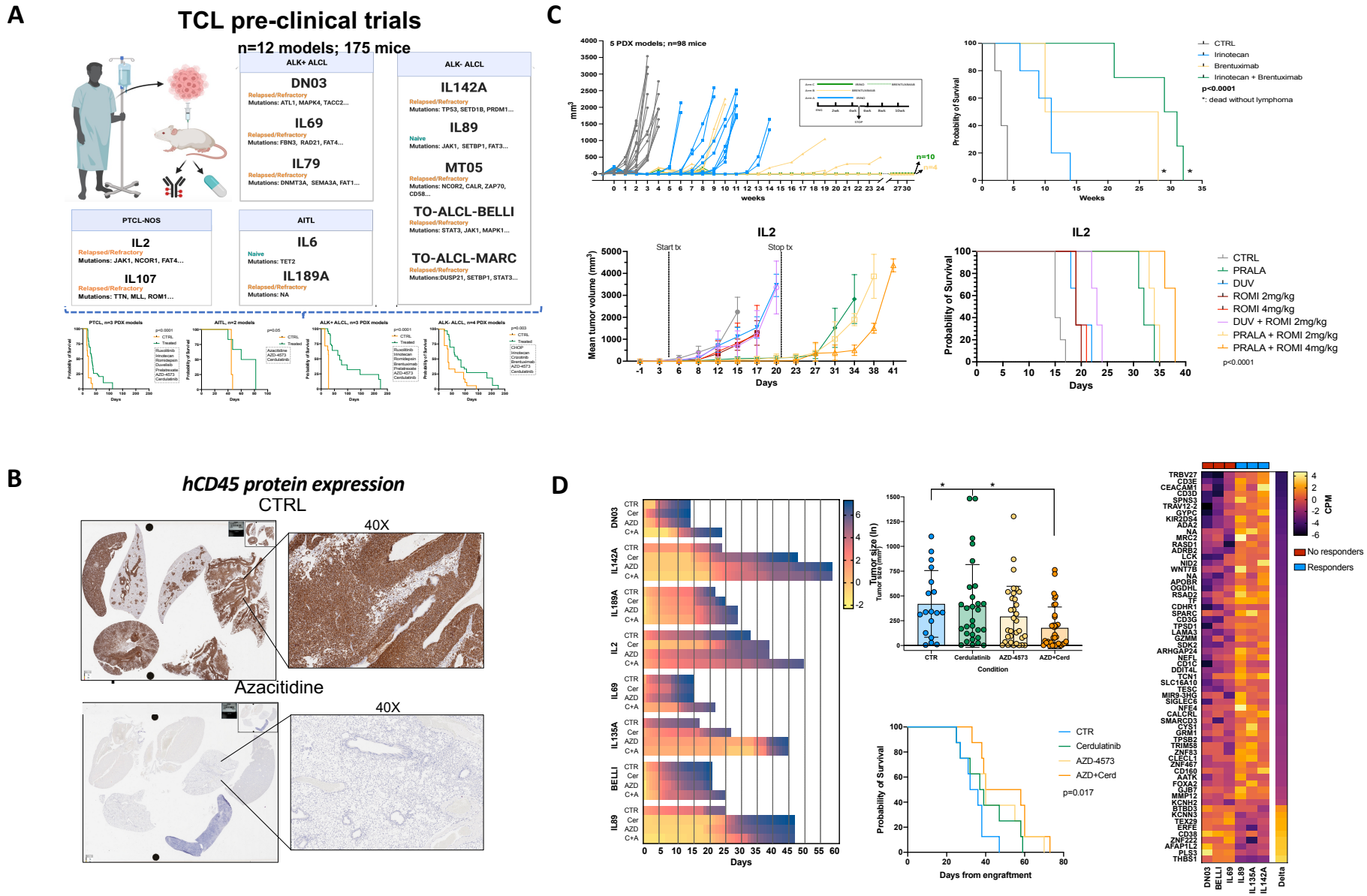
Tumor engraftments

Adjusted tailored therapies
to individual patient

Best individualized tumor therapies

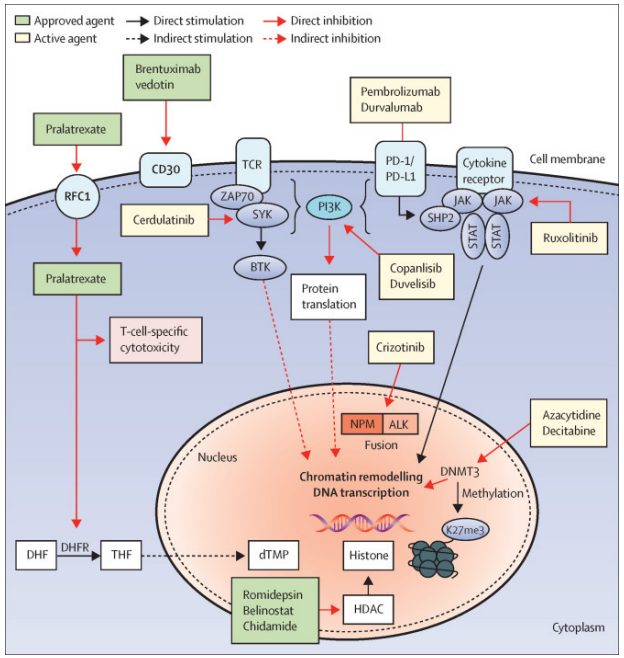
Multi-arm mouse's treatments

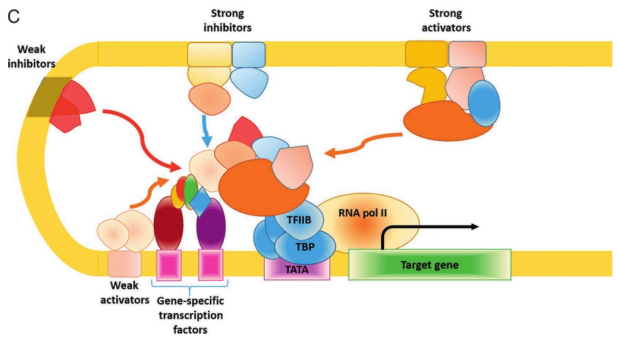
In vivo drug screening platform with PDTX libraries



Therapeutic potential of TFs degraders

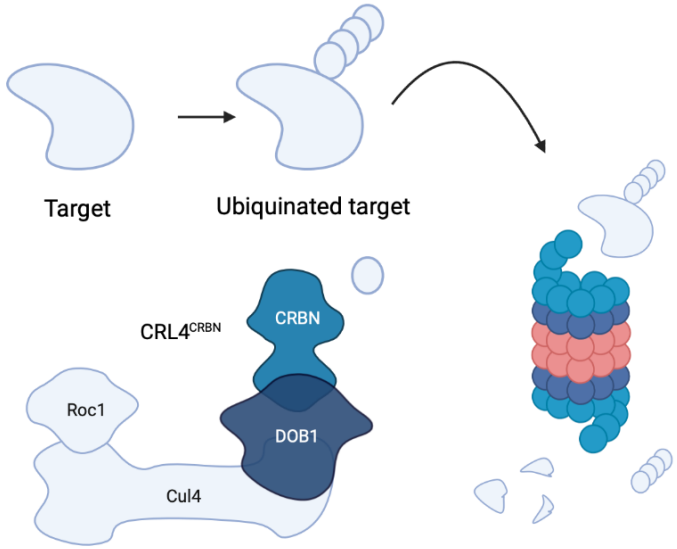
Current strategies

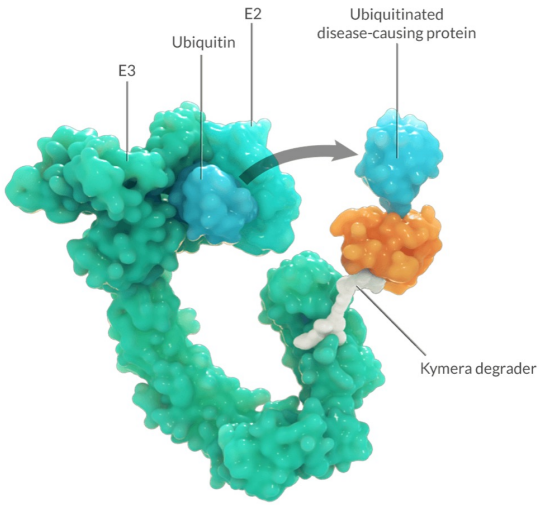




Untargetable proteins

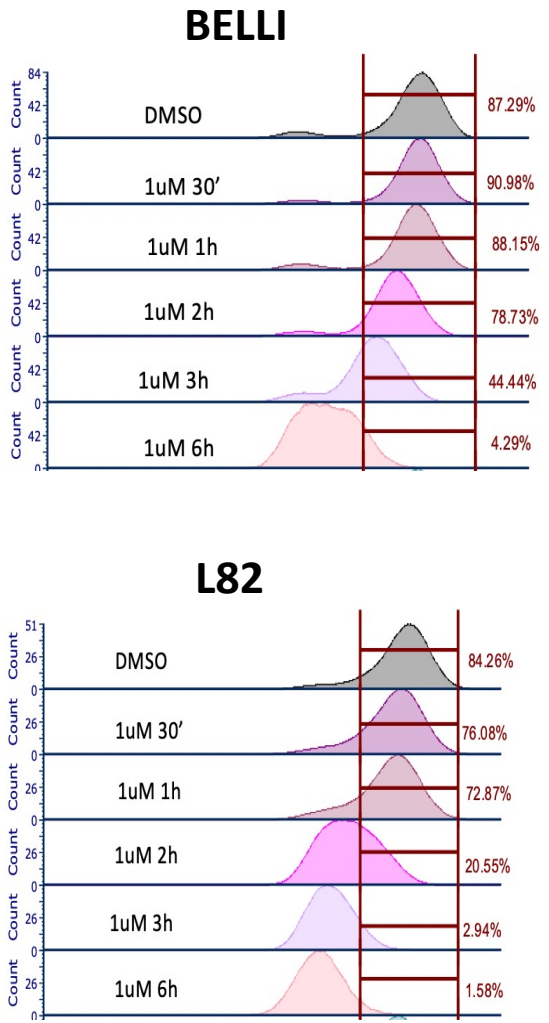
Future strategies



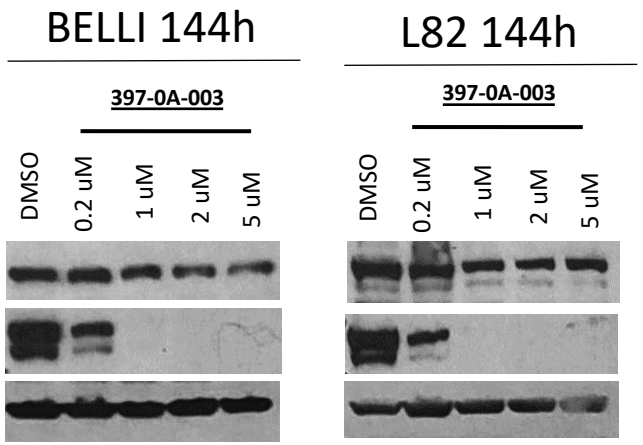


Pre-clinical therapeutics of STAT3 degraders

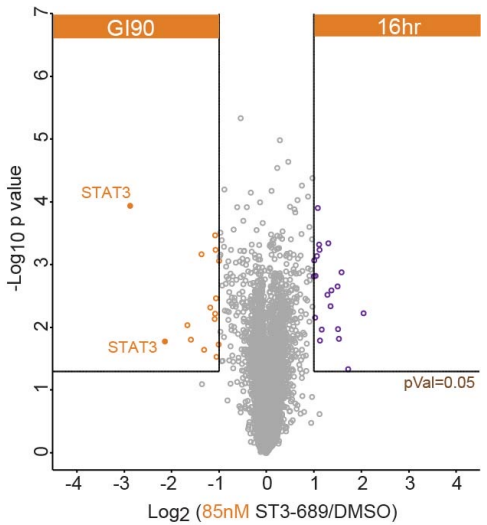
A



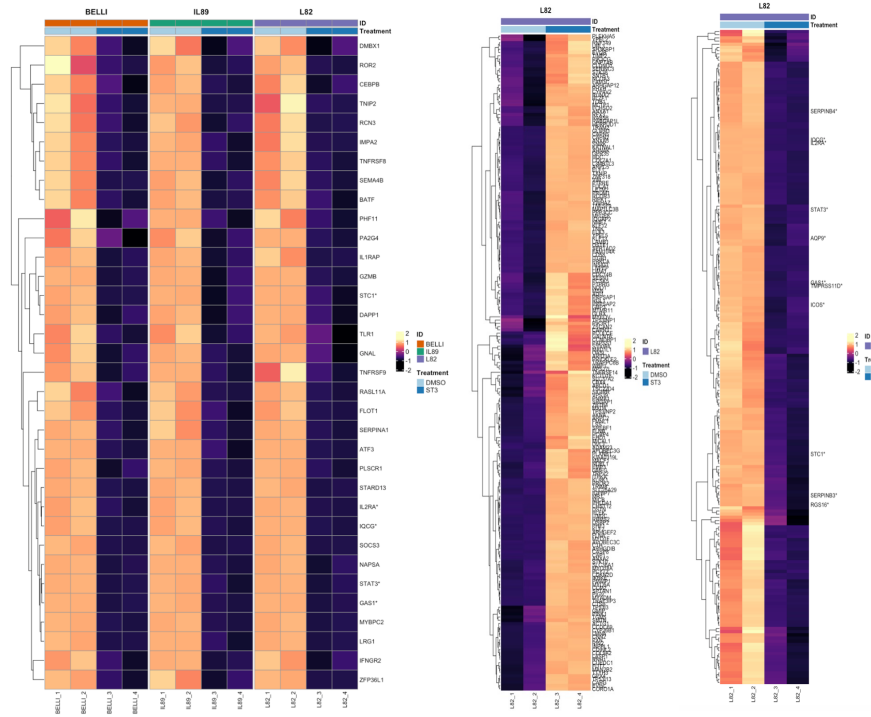
B



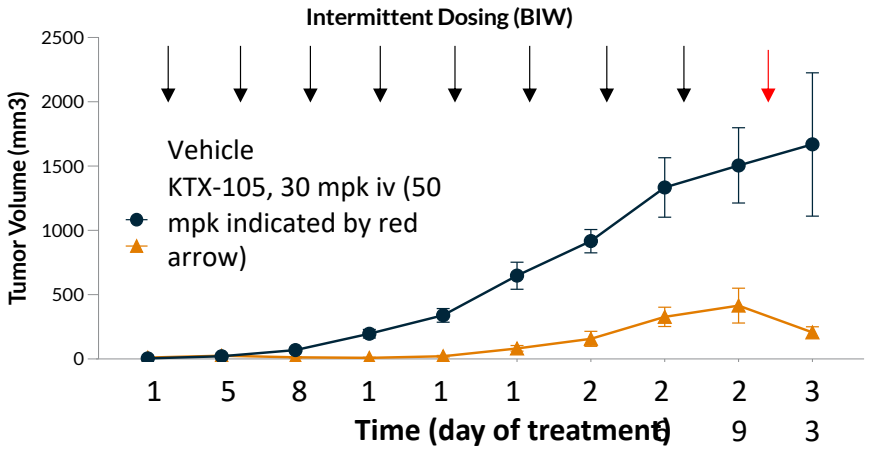
C



D



E

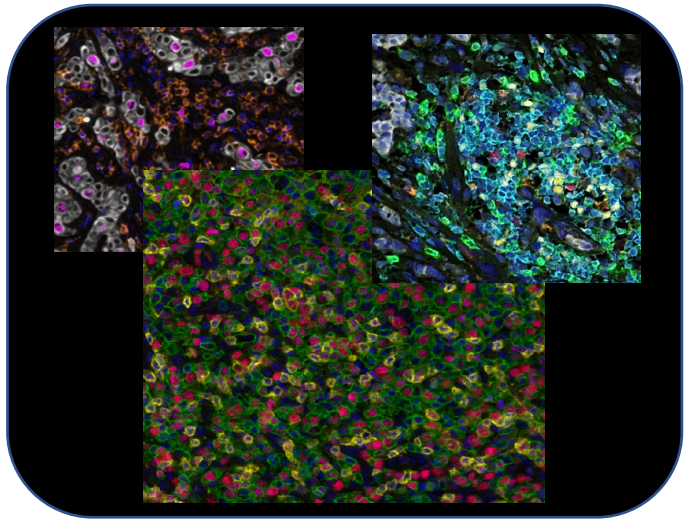


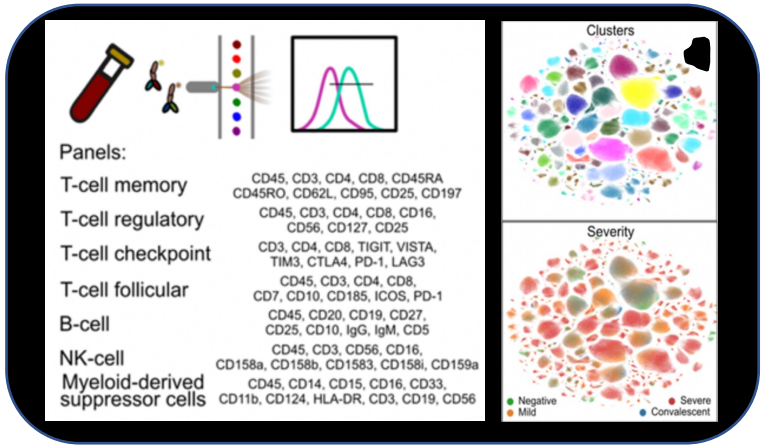
Astone G. et al. *Blood* (2021) 138 (Supplement 1): 865.

Where are we going?

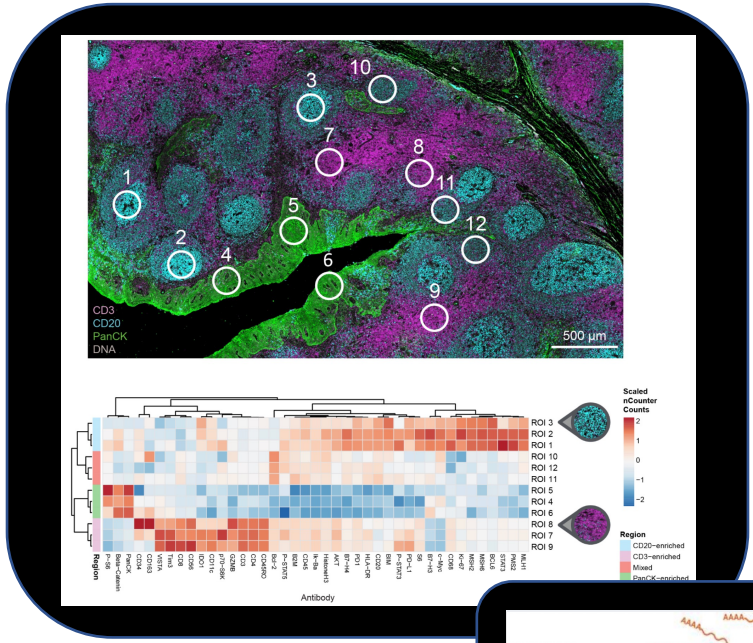
Multicolor flow cytometry & deep immune profiling

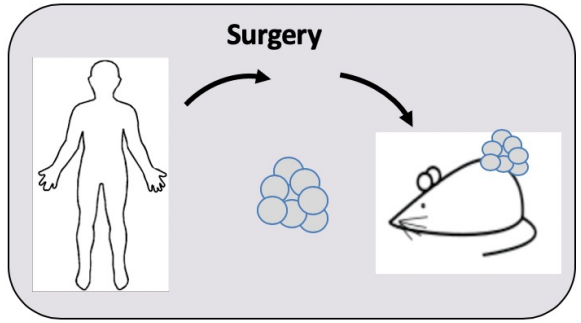
Multplex imaging

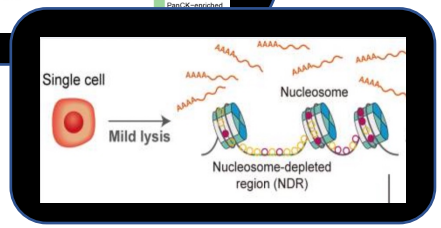




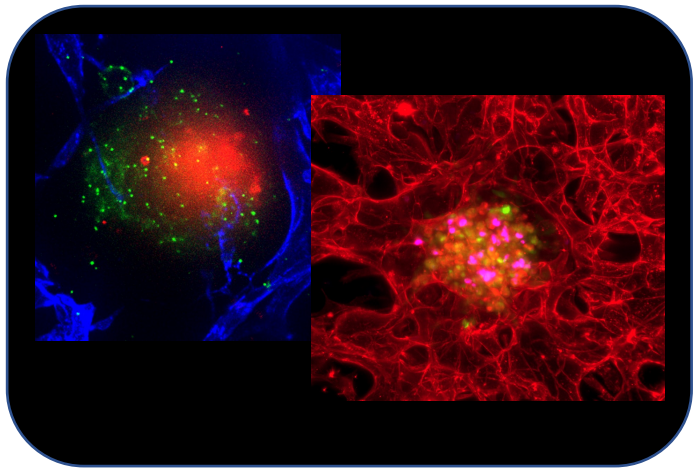
Digital Spatial Profiler



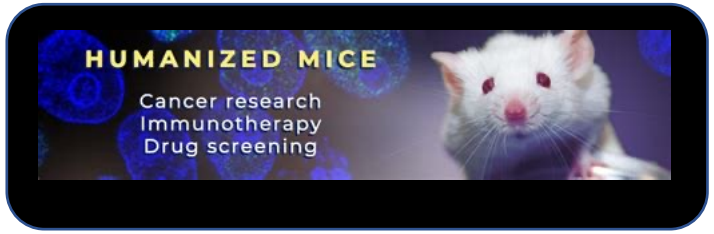




scChaRM-seq



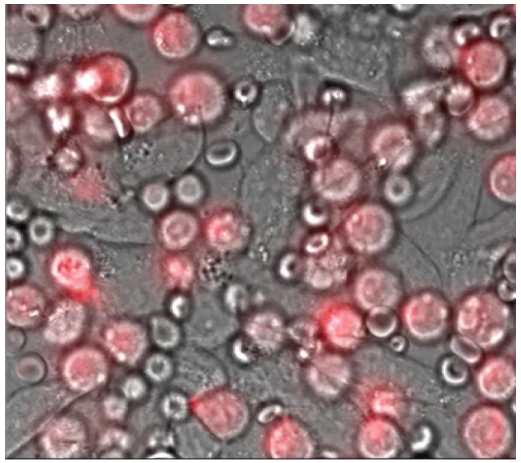
PDX and Organ-On-VascularNet

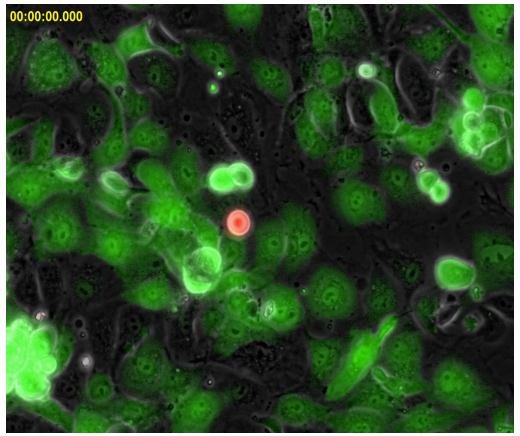


PDX in fully autologous humanize mice

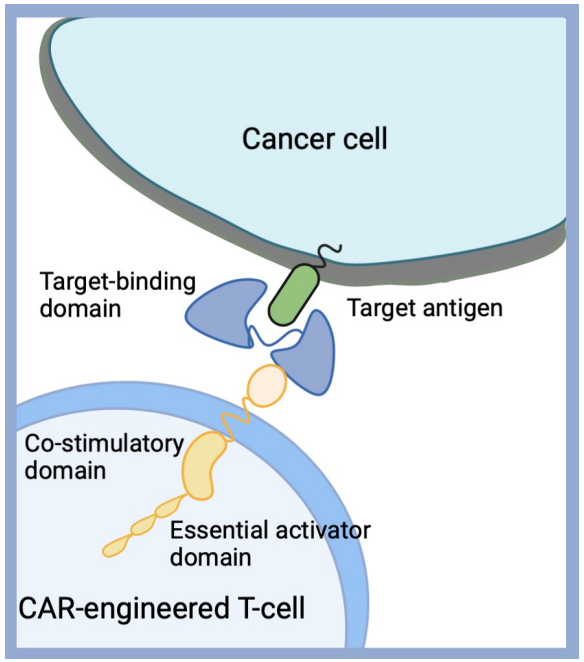
Naïve and engineered PDX derivatives

2D



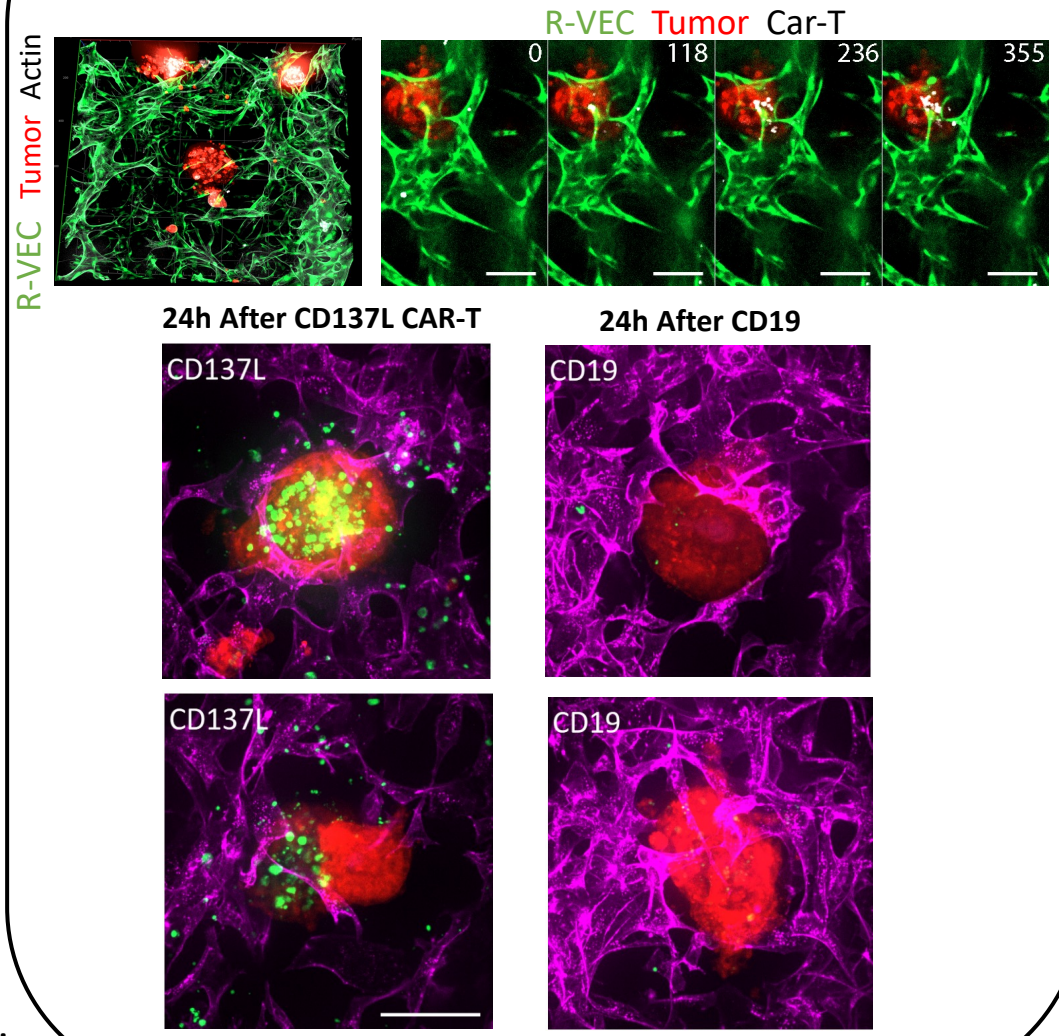


CAR-T cells



Tumor-On–VascularNET model

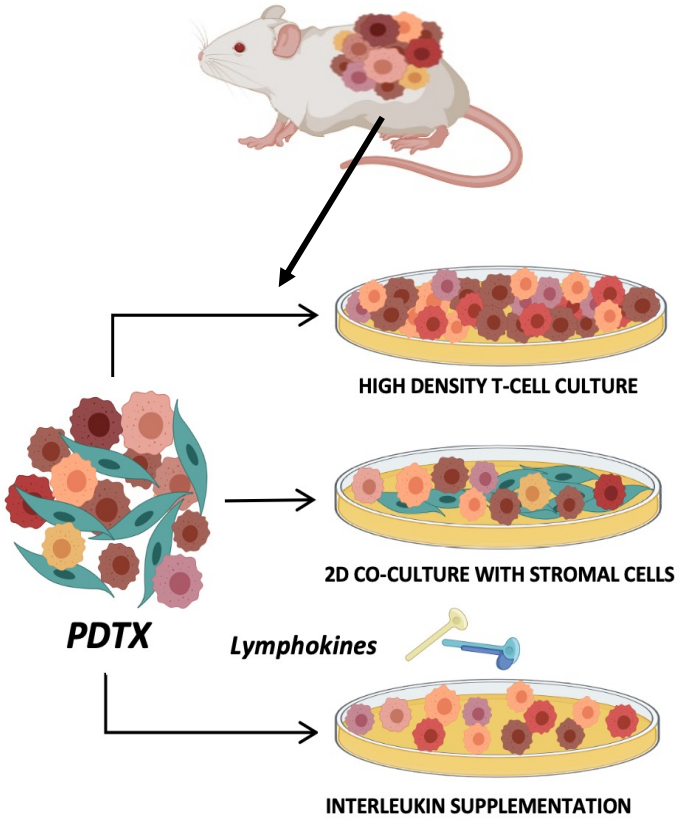
Microfluidic device

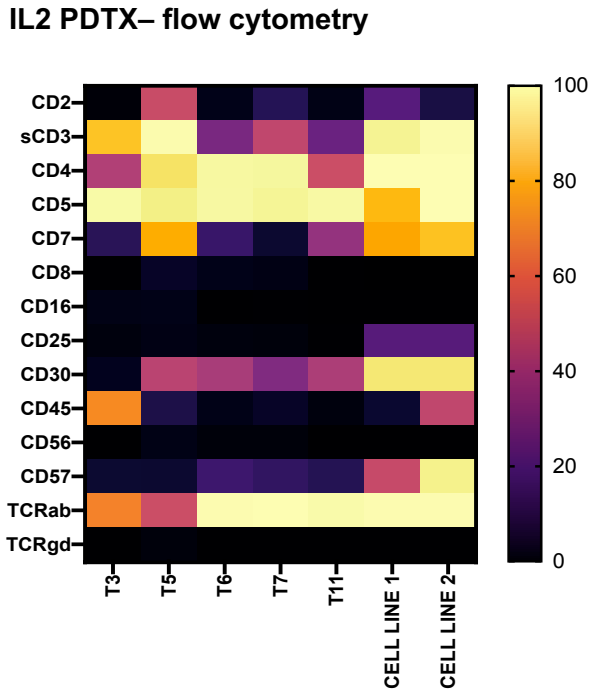


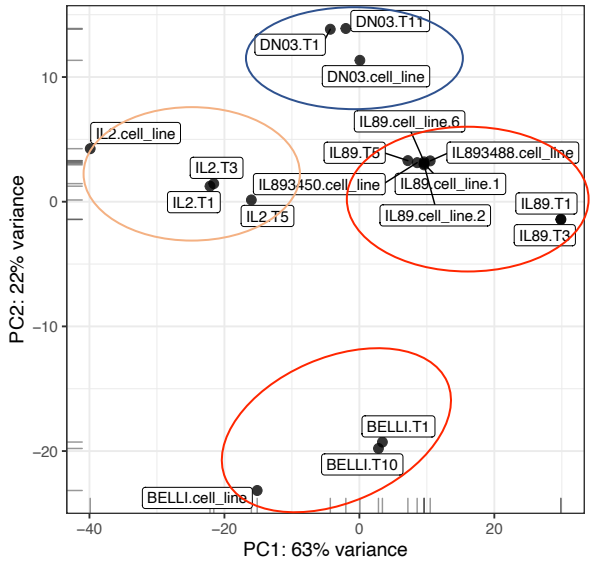
Weill Cornell Medicine

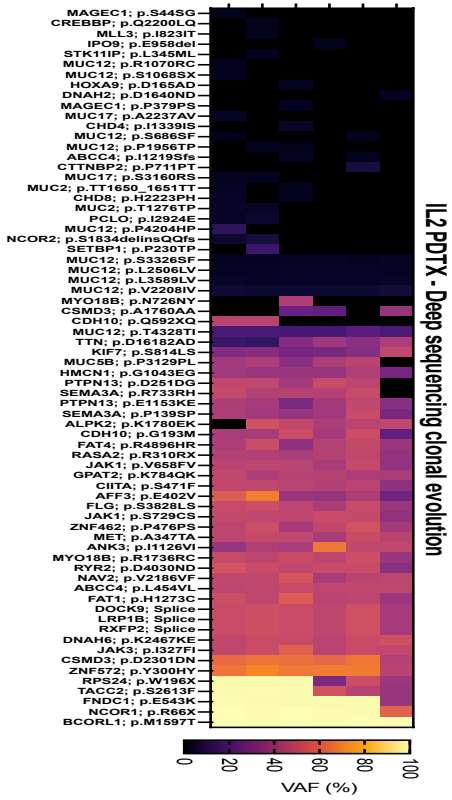
In collaboration with Dr. Shahin Rafii

PDX-D line for genomic and functional readouts

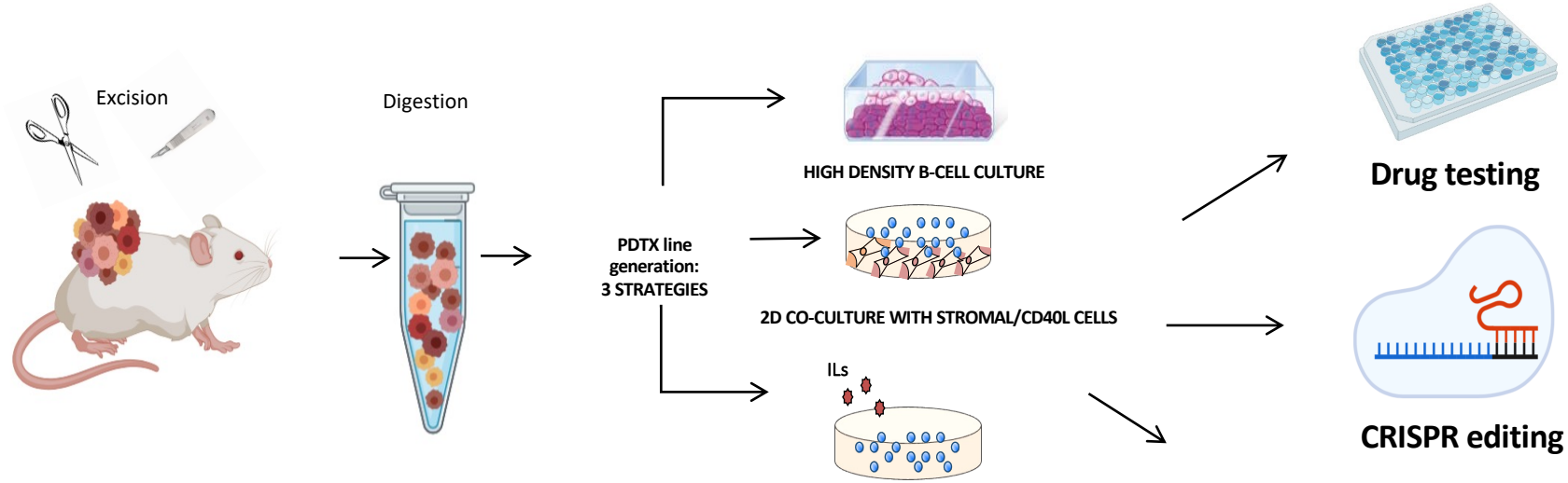


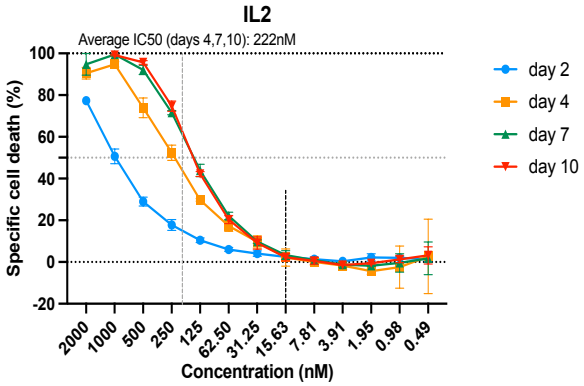


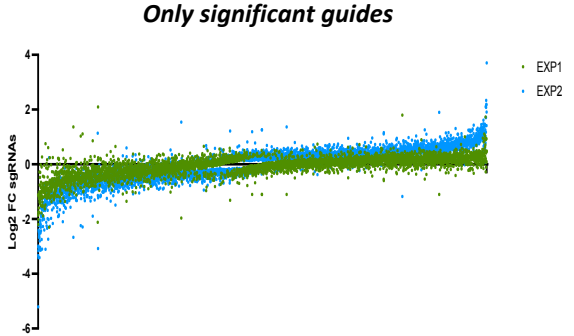




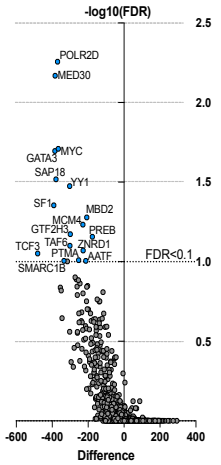
CRISPR screening to define PTCL vulnerabilities



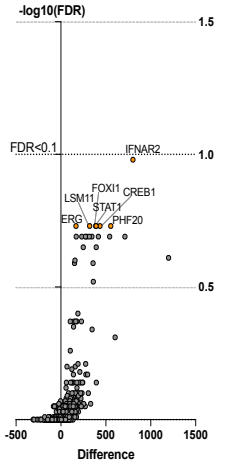




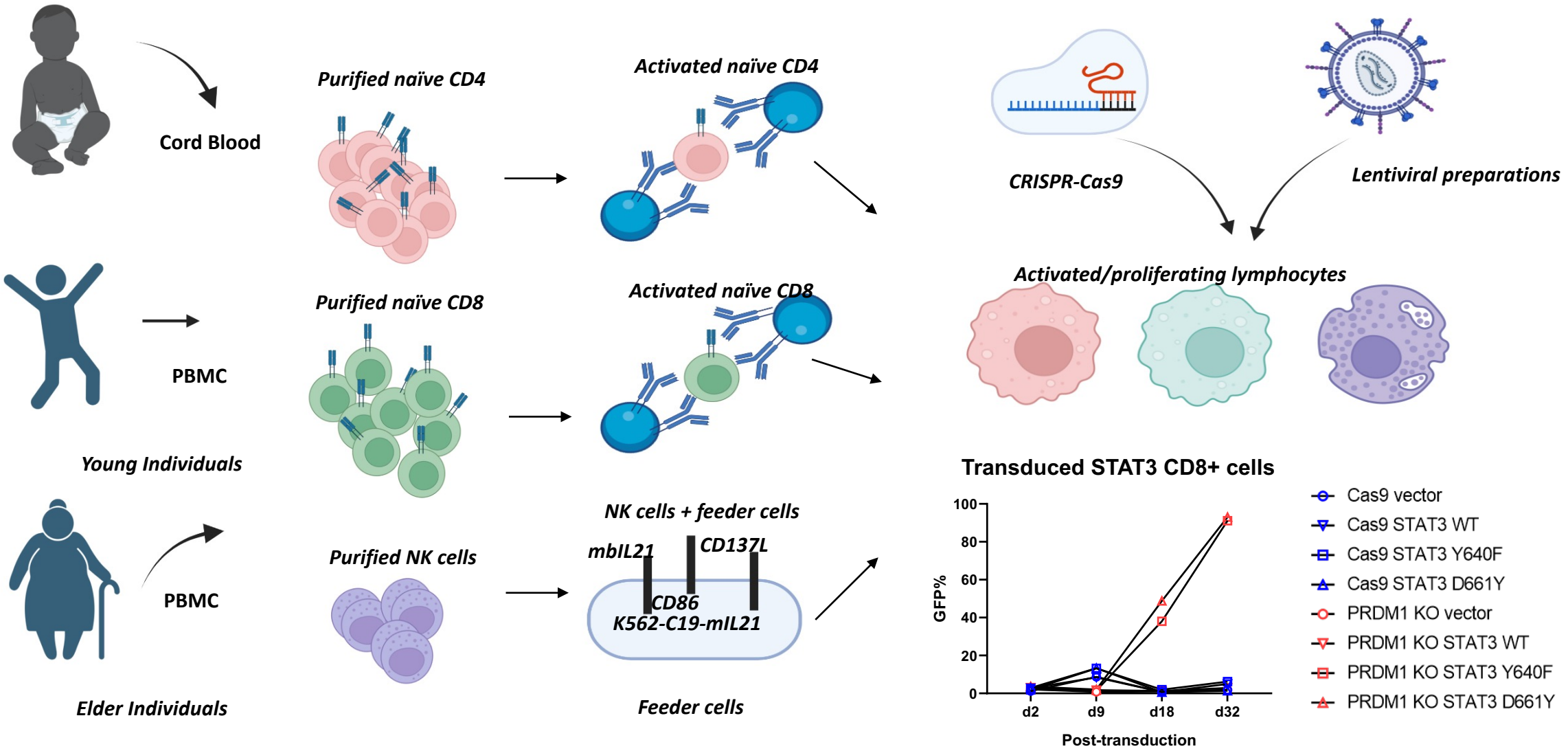
IL2 cell line untreated: exp 1+exp2



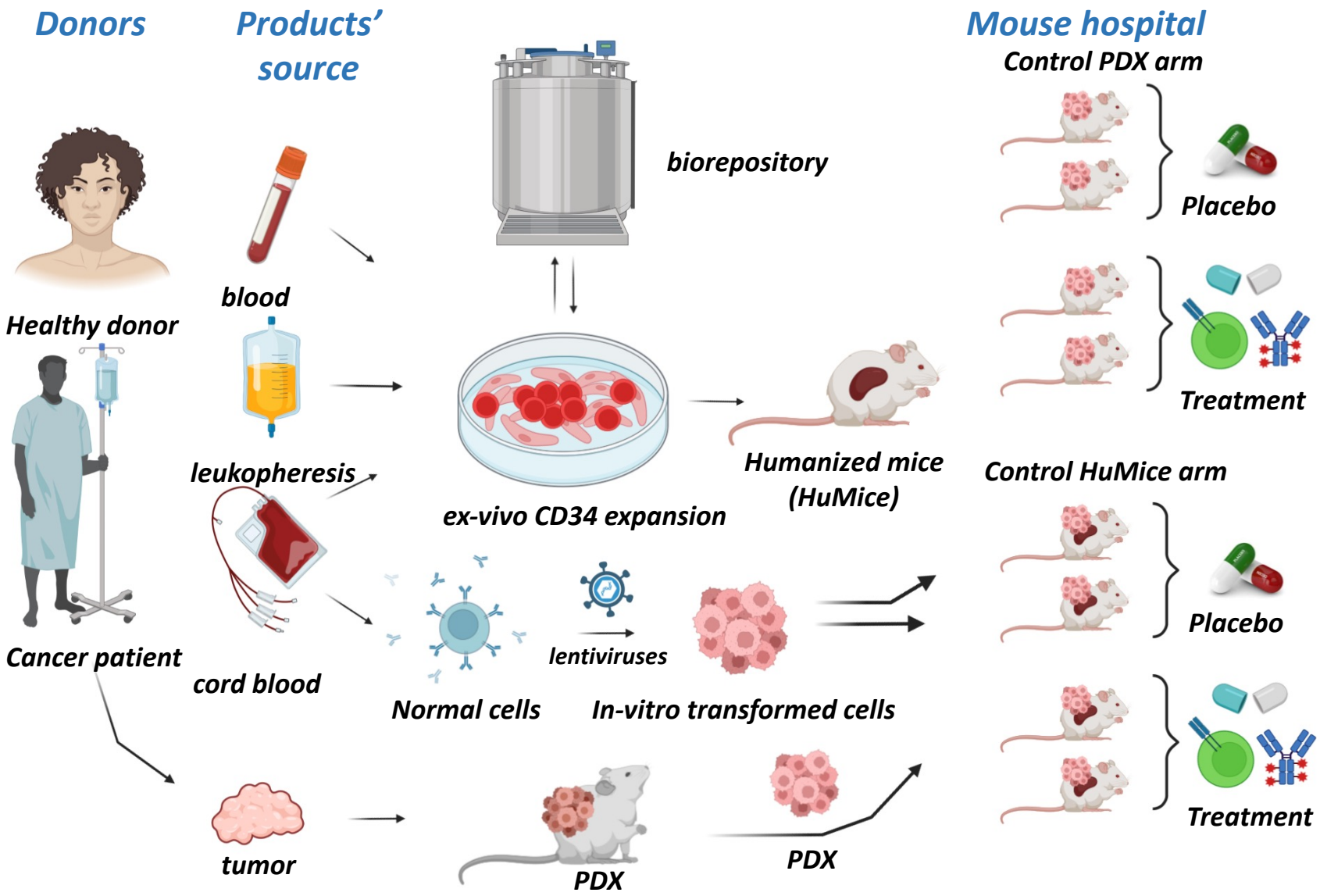
IL2 cell line w/wo ruxo



Engineered T-cells models



Humanized/engineered NSG mice strategies



Conclusions

- The construction of well-annotated PDTX lymphoma libraries required Institutional commitments and dedicated resources

- PDTX closely mimic corresponding matched donor samples, sharing genomic fingerprints and functional properties

- PDTX and PDTX derived products are practical tools for performing HTP screening and predict patients' specific vulnerabilities

- Host tumor interactions modulate lymphoma growth and survival and drug responses

- Autologous humanized PDTX represent the next frontier for the design and implementation of novel and immuno-based clinical protocols

Acknowledgements

Danilo Fiore
Luca V Cappelli
Maria Teresa Cacciapuoti
Giorgia Zanetti
Giuseppina Astone
Clarisse Kayembe
William Chiu
Liron Yoffe

Wayne Tam
Shahin Rafii
Joseph Scandura
Silvana Di Giandomenico

Leandro Cerchietti
Ari Melnick
Jude Phillips
Doron Betel
Paul Zumbo

Englander Institute for Precision Medicine
Olivier Elemento

Steven M. Horowitz
Alison Moskowitz
Andrew M. Intlekofer
Zachary D. Epstein-Peterson
Ahmed Dogan
Elisa de Stanchina
Inna Khodos

Larry Kwak
John Chan

Robin Foa'
Anna R. Guarini
Sabina Chiaretti

Monica Maccagno
Roberto Piva

David M. Weinstock
Samuel Ng
Jon C. Aster

Raul Rabadan
Francesco Abate
Zhaoqi Liu
Francesco Brundu

Nikita Kotlov,
Anton Karelin,
Maria Sorokina
Sandrine Degryse


THANK YOU
Weill Cornell Medical College