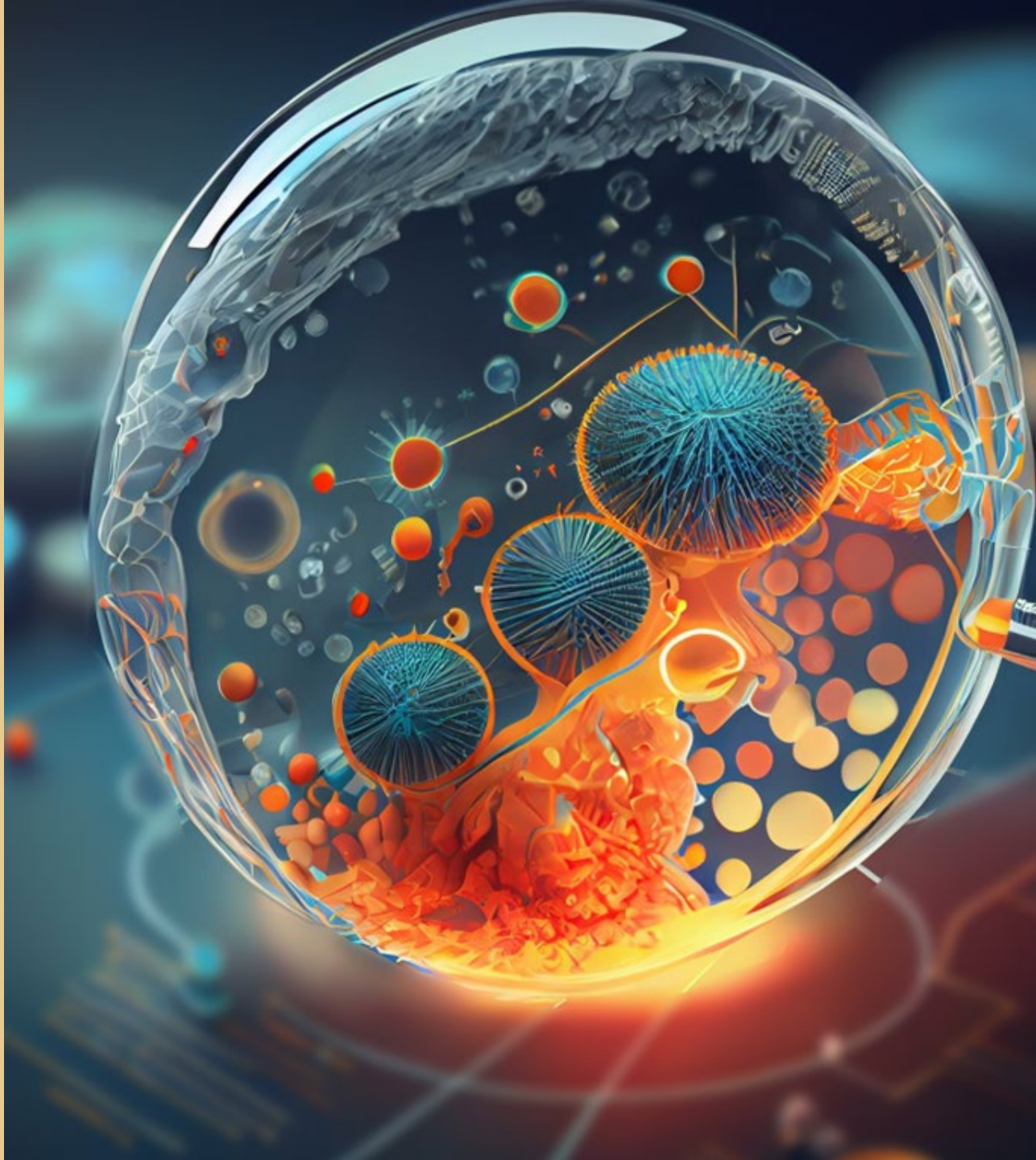
eha Sf(PM)

From single-cell profiling to effective drug combinations

Applications to solid and hematological cancers



September 26, 2024
Tero Aittokallio, PhD

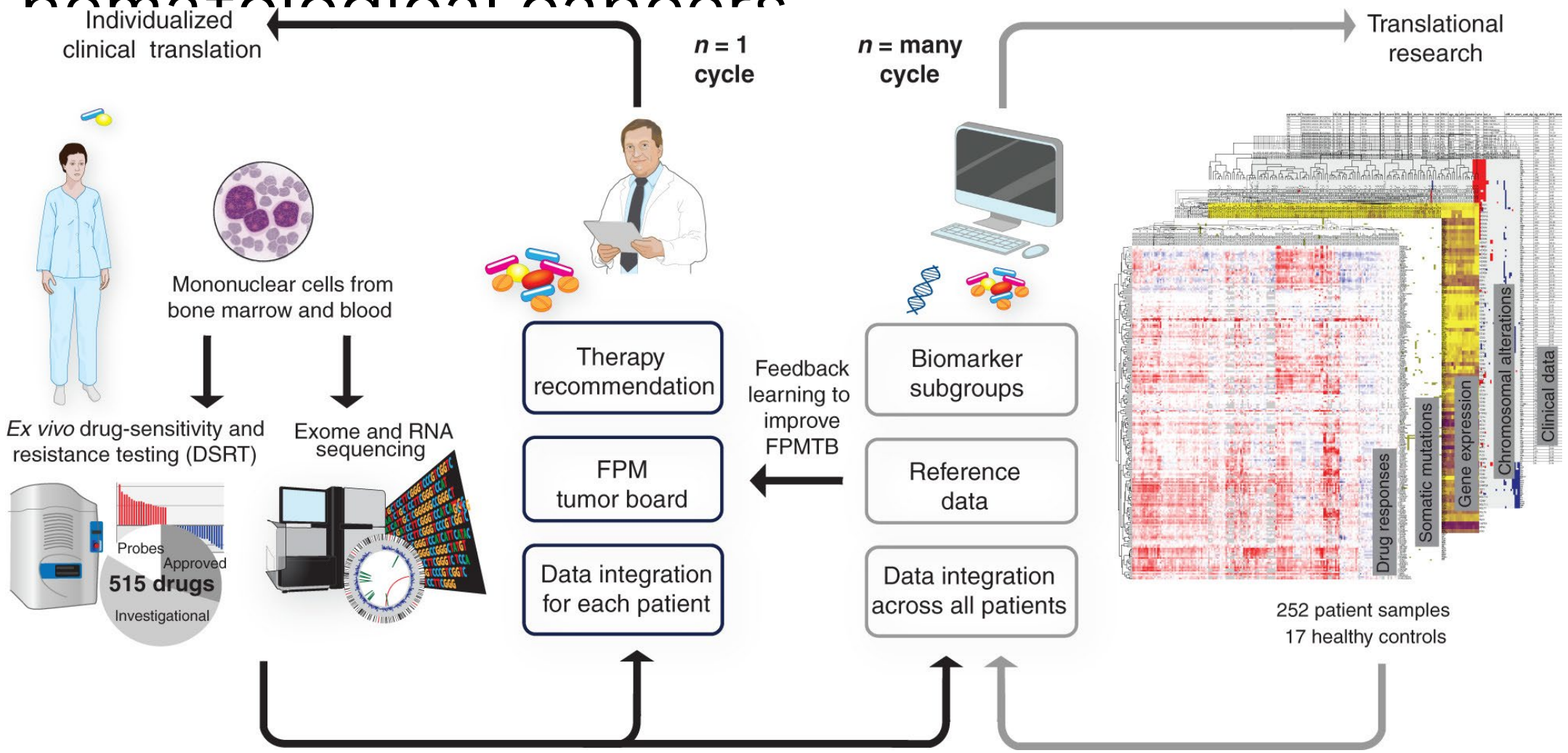
Contents

eha Sf(PM)

Tero Aittokallio, PhD
Group Leader, Institute for Cancer Research, Oslo University Hospital
Professor, OCBE, Department of Biostatistics, University of Oslo
Group Leader, Institute for Molecular Medicine, University of Helsinki
Visiting Professor, InFLAMES Research Flagship, University of Turku

Disclosures: None

Functional precision medicine for hematological cancers



AML
T-PLL
CLL
CML

HUS FIMM iCAN HRUH HEMATOLOGY RESEARCH UNIT HELSINKI

Malani et al. Cancer Discovery 2022

Current clinical and computational challenges

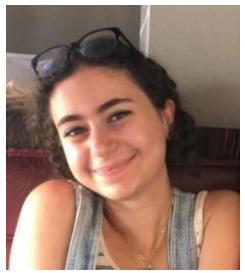
1) Modeling the effect of cellular heterogeneity of cancer sub-clones on clinical outcomes (e.g. treatment responses)

2) Identification of synergistic drug combinations that inhibit multiple cancer driving pathways and sub-populations

3) Mining of clinical, functional, and genomic biomarkers that are predictive of (combination) treatment responses

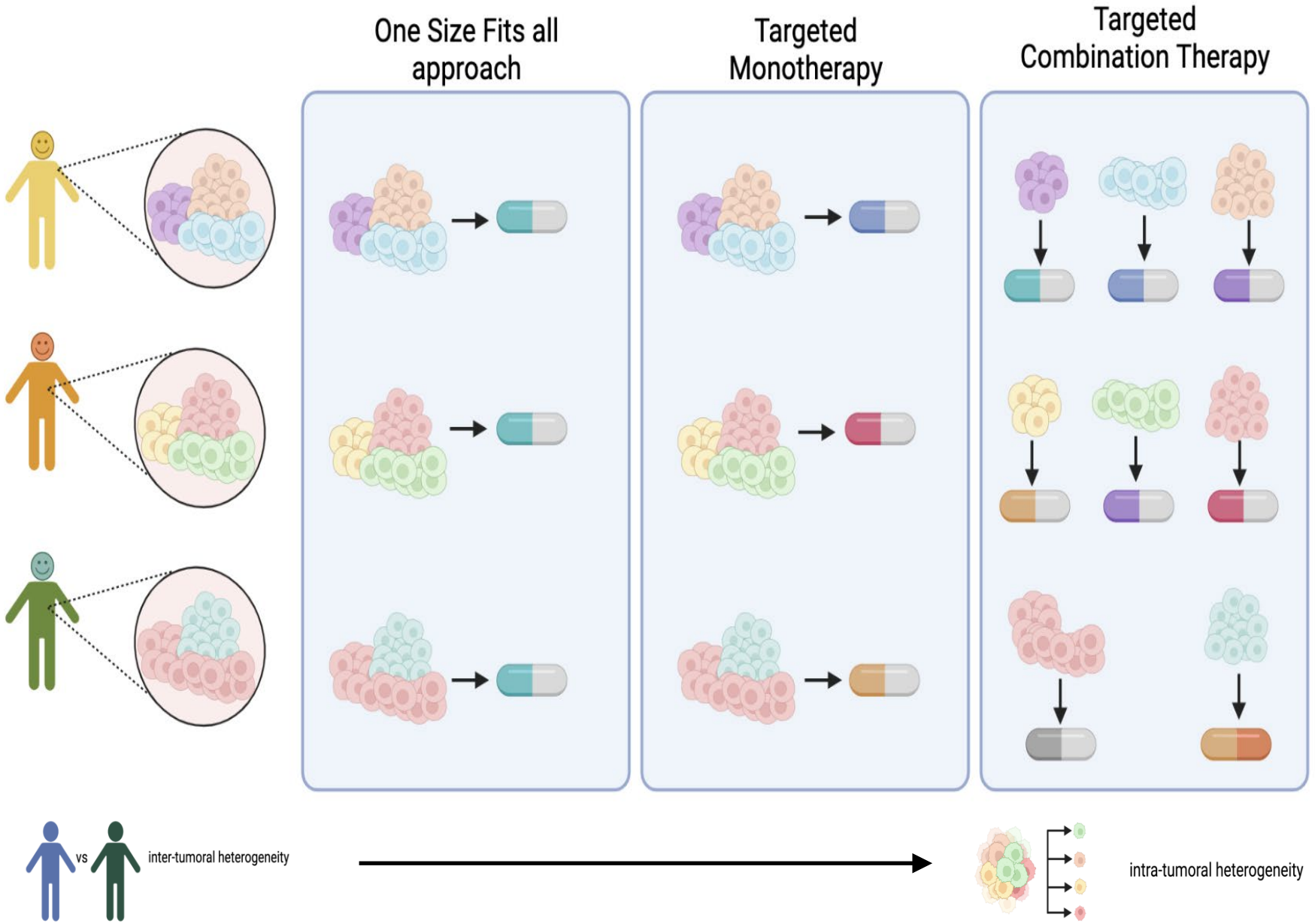
Response predictive biomarkers

Optimal therapy options for each individual patient



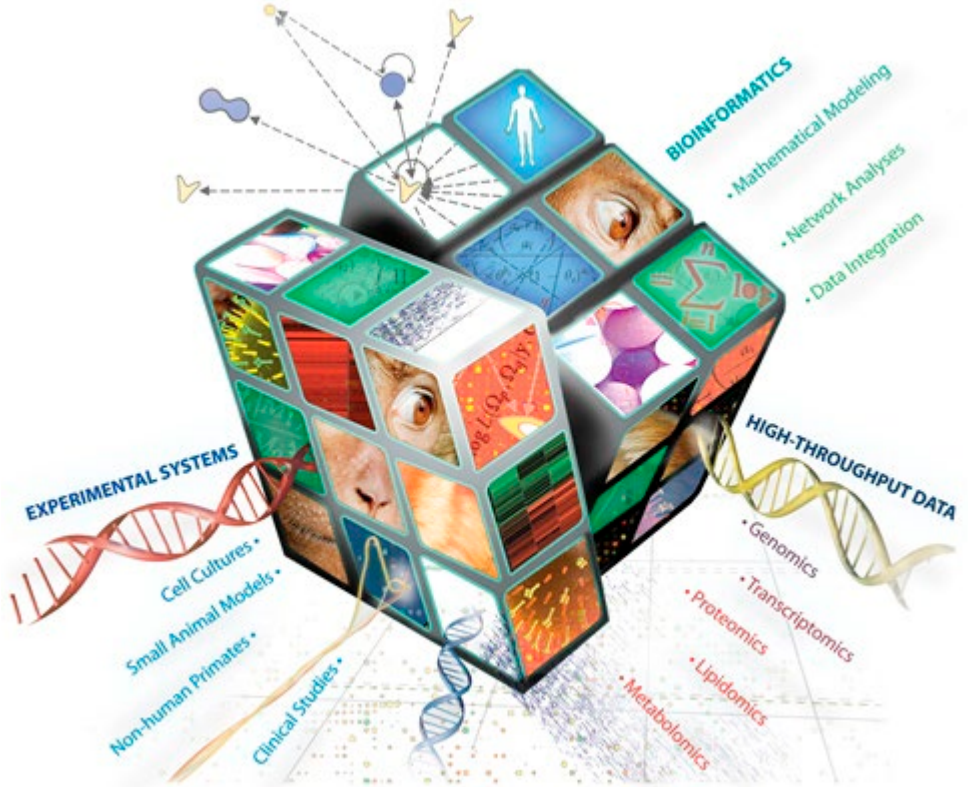
Kristen Nader

Targeted cancer therapy and tumour heterogeneity



AI-guided treatment selection?

Multi-modal modelling!



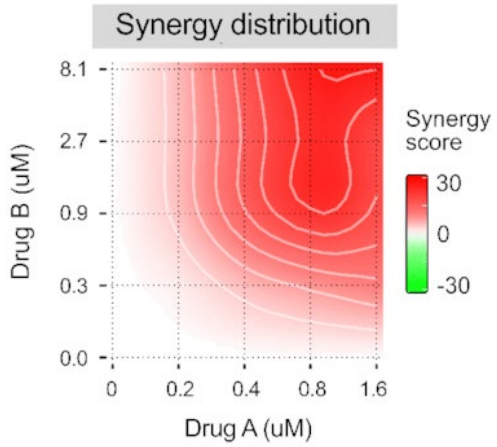
Credit: A2IDEA

How to identify successful drug combinations?

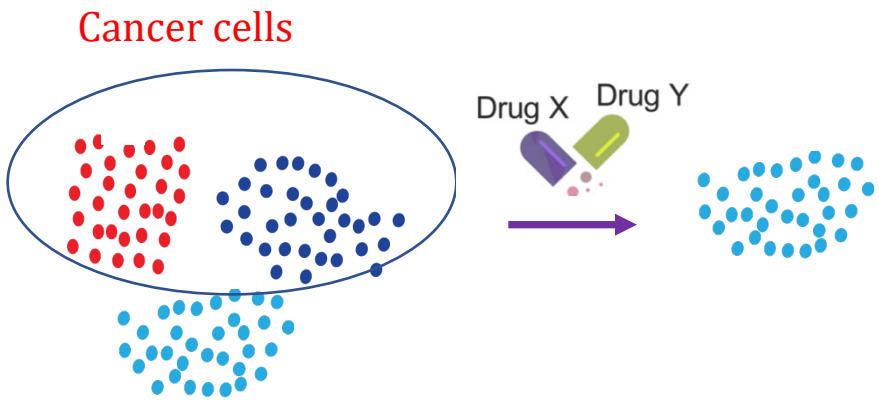
Anil Kumar Giri

Effective

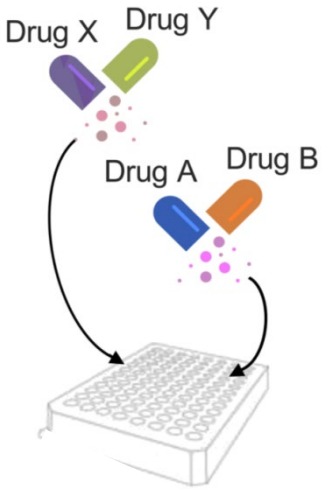
Synergistic



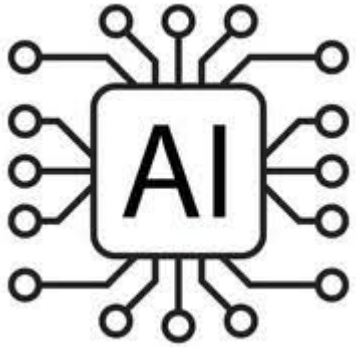
Cancer cell selective (less toxic)



Testing in patient-derived cells



Scarce primary cells

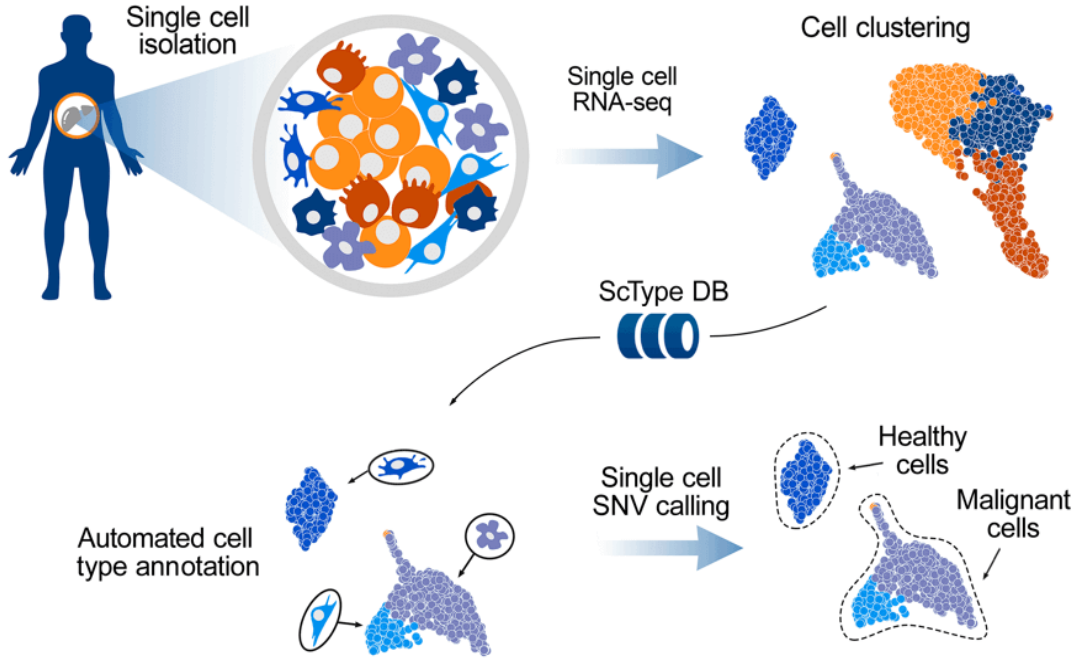


ScType web-app and marker database for fully-automated and ultra-fast cell type identification

Aleksandr Ianevski

Input data

scRNA-seq expression matrix



Output

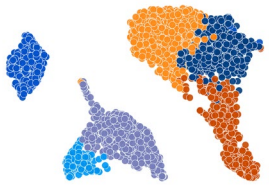
Automated cell type annotations

https://sctype.app

> 270 citations

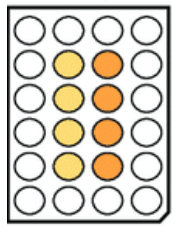
Ianevski et al., Nat Comm 2022

ML algorithm to tailor drug combinations for individual patients



Single-cell RNA-seq

+



Ex-vivo drug response to single compounds

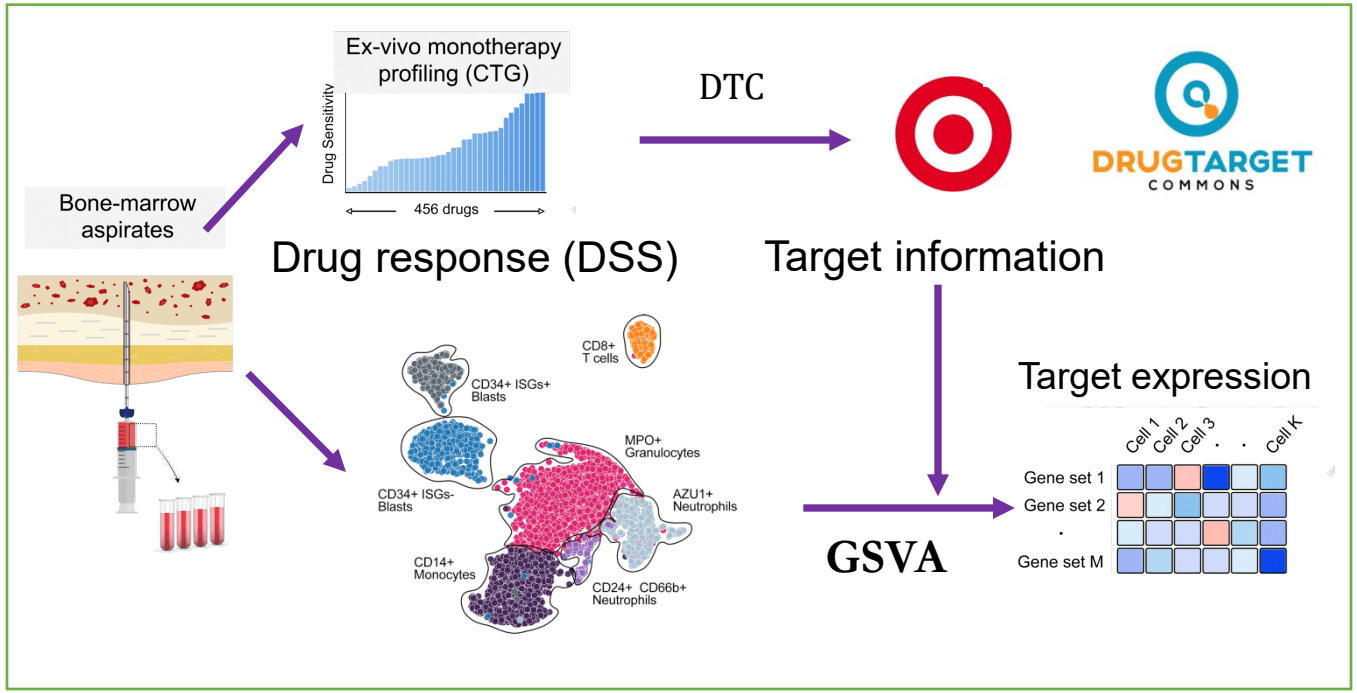
+

XGBoost

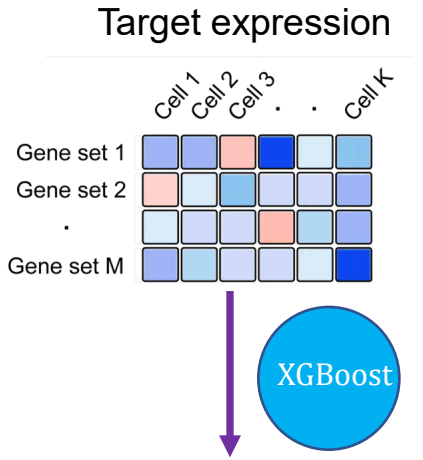
Machine learning

Patient-specific drug combinations

Data processing



Machine learning

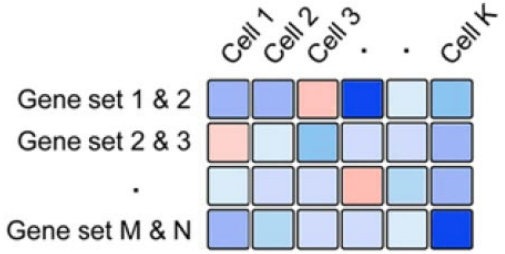


Outcome: DSS profile for each patient sample

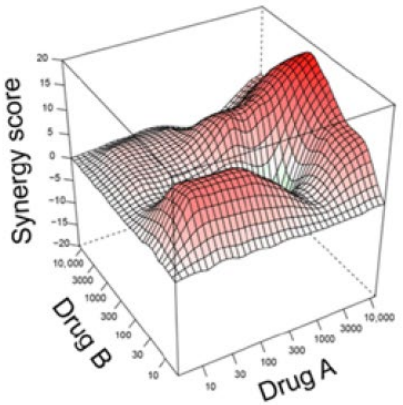
Chen et al. Nat Protoc 2024

Patient-specific testing using *ex vivo* drug testing assays

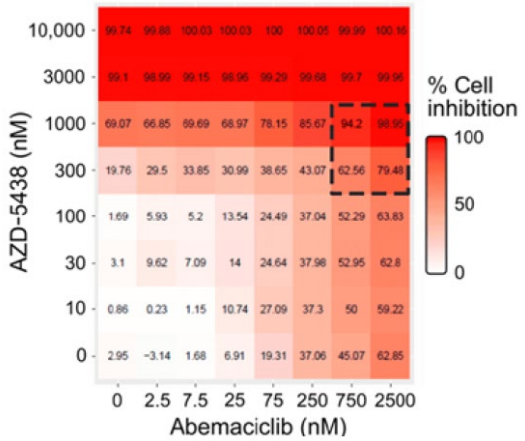
GSVA of drug combination target gene sets



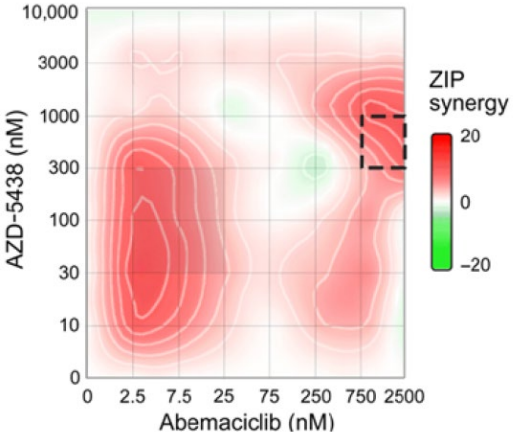
Prediction of synergistic, potent, and low-toxicity combinations



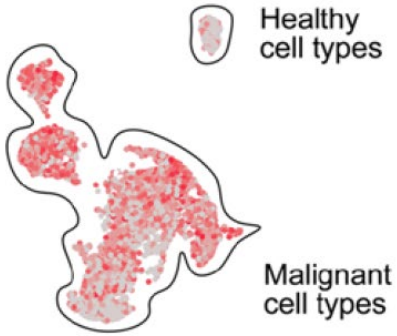
Dose-response matrix



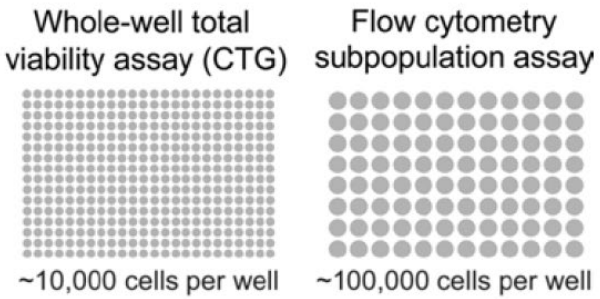
Synergy distribution



Combination target expression in malignant and healthy cells



Experimental validation of top predicted combinations



Ianevski et al., Science Advances 2021

Prediction of patient-specific drug combinations in 4 longitudinal AML samples

Table 1. Clinical and molecular characteristics of the patients with AML and samples. Flow cytometry–based clinical immunophenotyping was performed in fresh red blood cell–depleted bone marrow samples at Helsinki University Hospital, whereas the scRNA-seq profiling was done on the basis of thawed Ficoll-treated and cryopreserved AML cells at the FIMM (Institute for Molecular Medicine Finland) Single-Cell Unit. The blast percentages differ between the two readouts because of different cell isolation protocols and different blast identification approaches. ICD-O, International Classification of Diseases for Oncology.

Patient sample	Disease stage	Age	Sex	scRNA-based blast (%)	Clinical morphological blast (%)	Diagnosis (ICD-O)	FAB type*	Previous malignancies or predisposing conditions	Risk class at the time of diagnosis	Potential driver mutations	Treatment history
AML1_D	Diagnosis	35	M	68	65	AML, C92, 9874	M2	No	Low	*WT1*, *CCND2*, and *CEBPA*	Cytarabine-idarubicin, lenalidomide
AML2_R	Refractory	68	M	26	40	AML C92, 9920	NA	Non-Hodgkin's lymphoma	Intermediate	*DNMT3A*, *ERG*, *U2AF1*, and *BCOR*	Cytarabine-idarubicin, azacytidine
AML3_D	Diagnosis	70	F	35	70	AML C92	M1	Non-Hodgkin's lymphoma	Intermediate	*NPM1* and *TET2*	Azacitidine
AML3_R	Refractory	71	F	56	42	AML, C92	M1	Non-Hodgkin's lymphoma	Intermediate	*NPM1*, *TET2*, and *HDAC 1,2,7*	Azacitidine-venetoclax

*FAB, the French-American-British classification.

Ianevski et al., Science Advances 2021

SCIENCE ADVANCES | RESEARCH ARTICLE

CANCER

Patient-tailored design for selective co-inhibition of leukemic cell subpopulations

Aleksandr Ianevski[1,2], Jenni Lahtela[1], Komal K. Javarappa[1], Philipp Sergeev[1], Bishwa R. Ghimire[1], Prson Gautam[1], Markus Vähä-Koskela[1], Laura Turunen[1], Nora Linnavirta[1], Heikki Kuusanmäki[1,3,4], Mika Kontro[4], Kimmo Porkka[5], Caroline A. Heckman[1], Pirkko Mattila[1], Krister Wennerberg[1,3]*, Anil K. Giri[1]*, Tero Aittokallio[1,2,6,7]*

Source codes available at
https://github.com/IanevskiAleksandr/scComb

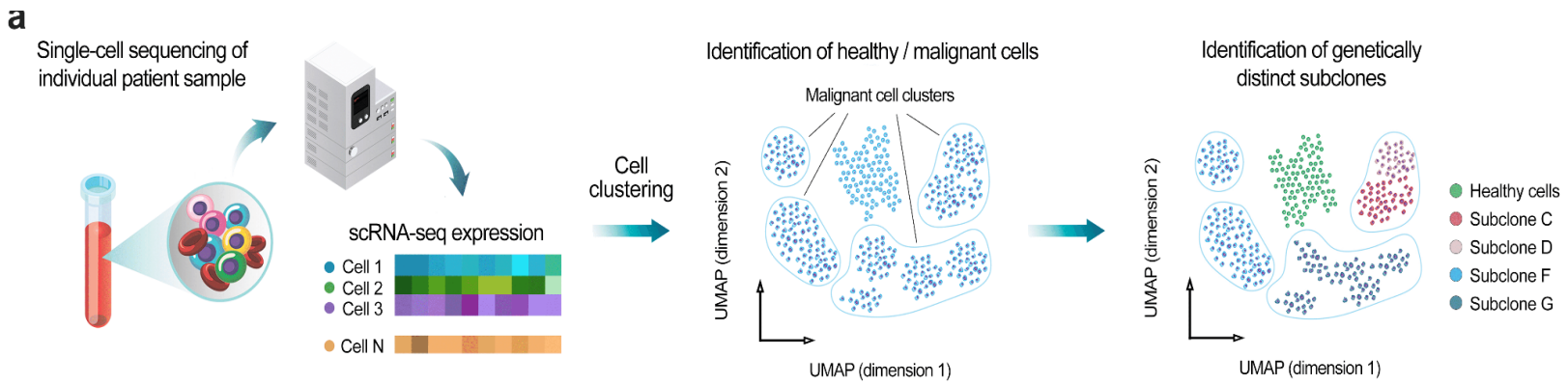
Current developments

- Selective combination predictions using scRNA-seq data alone
- Applications to solid tumors (high-grade serous carcinoma patients)
- Combination testing in more advanced assays (organoids, PDX)

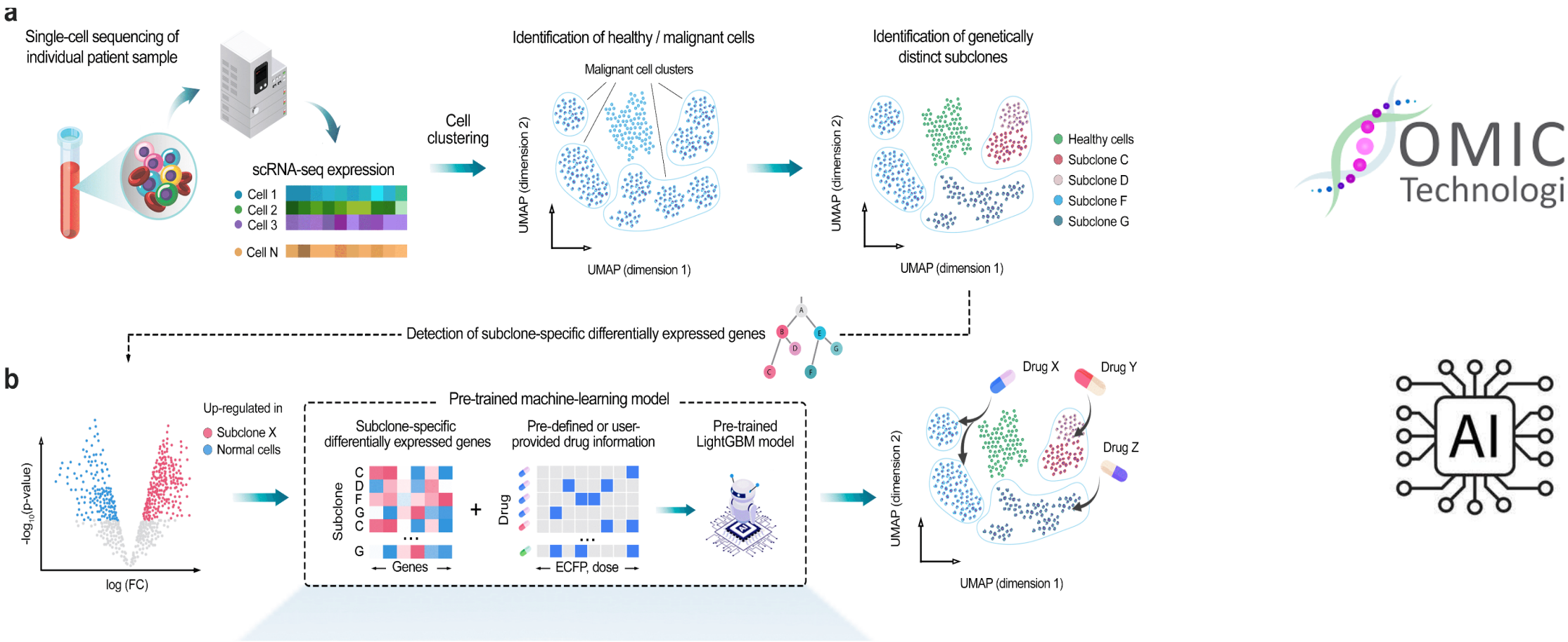
Patient-tailored therapies for selective co-inhibition of multiple cancer clones using single-cell transcriptomics alone

Ianevski, Nader, et al. Nature Communications, to appear

https://www.biorxiv.org/content/10.1101/2023.06.26.546571v1

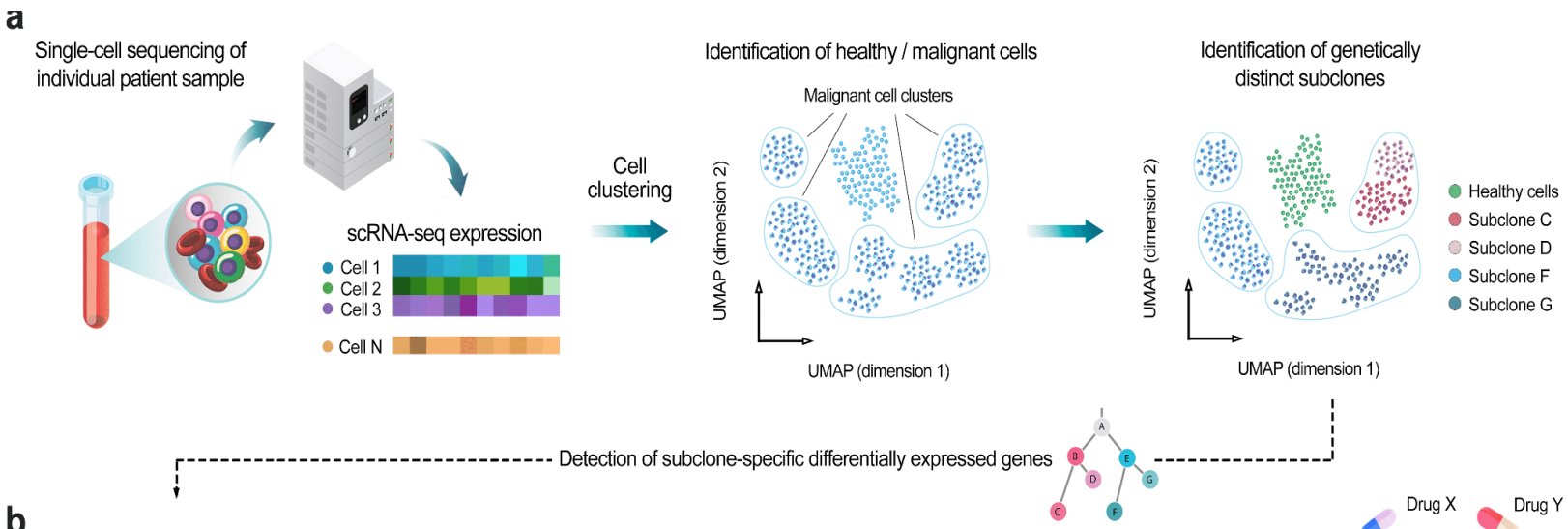


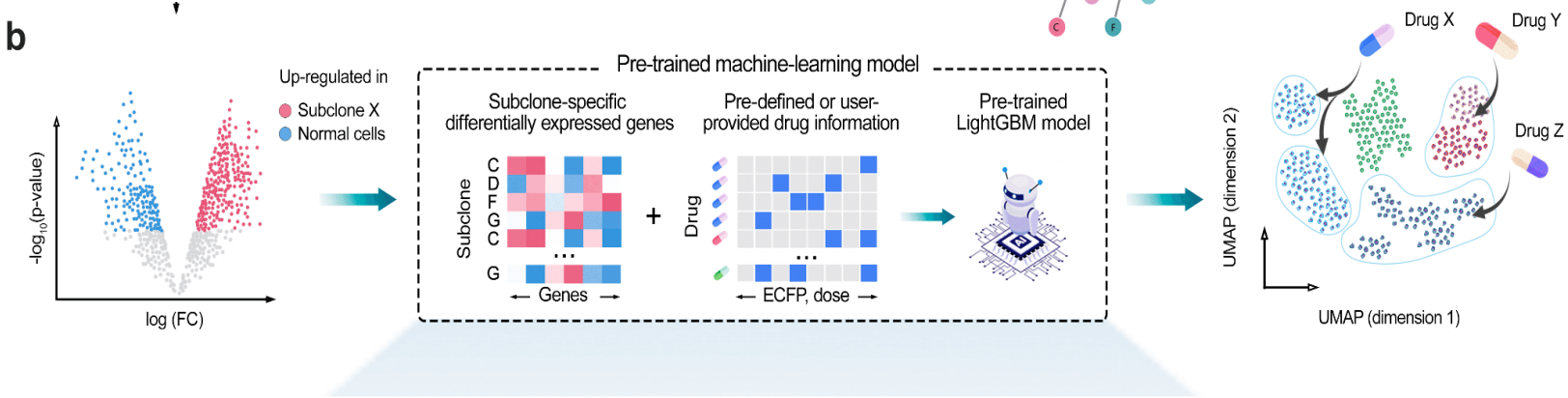
OMICS Technologies

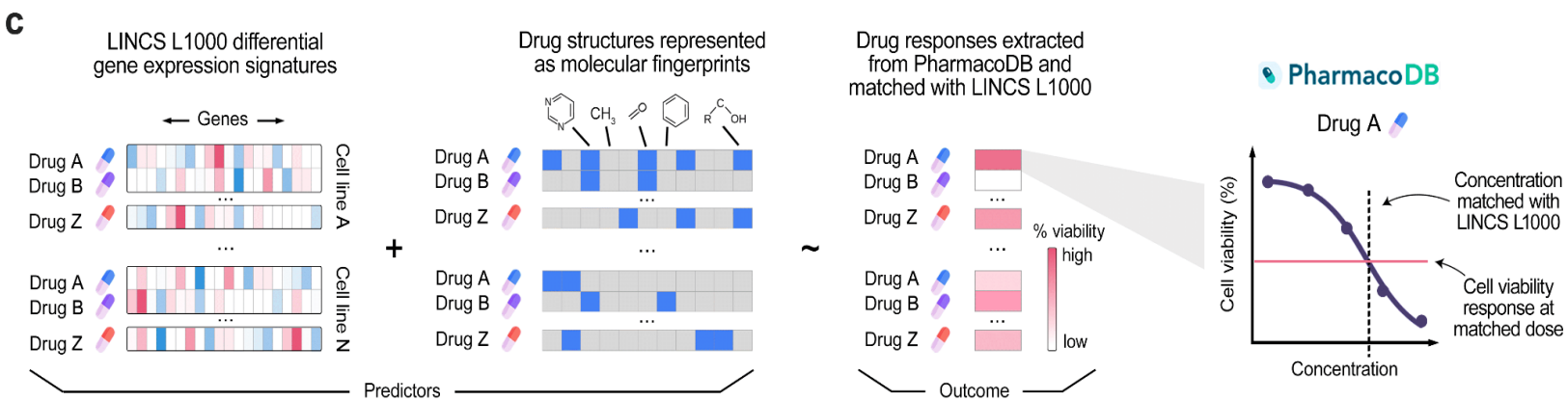


OMICS Technologies

AI


a
Single-cell sequencing of individual patient sample
scRNA-seq expression
Cell 1
Cell 2
Cell 3
Cell N
Cell clustering
Identification of healthy / malignant cells
Malignant cell clusters
UMAP (dimension 2)
UMAP (dimension 1)
Identification of genetically distinct subclones
Healthy cells
Subclone C
Subclone D
Subclone F
Subclone G
Detection of subclone-specific differentially expressed genes

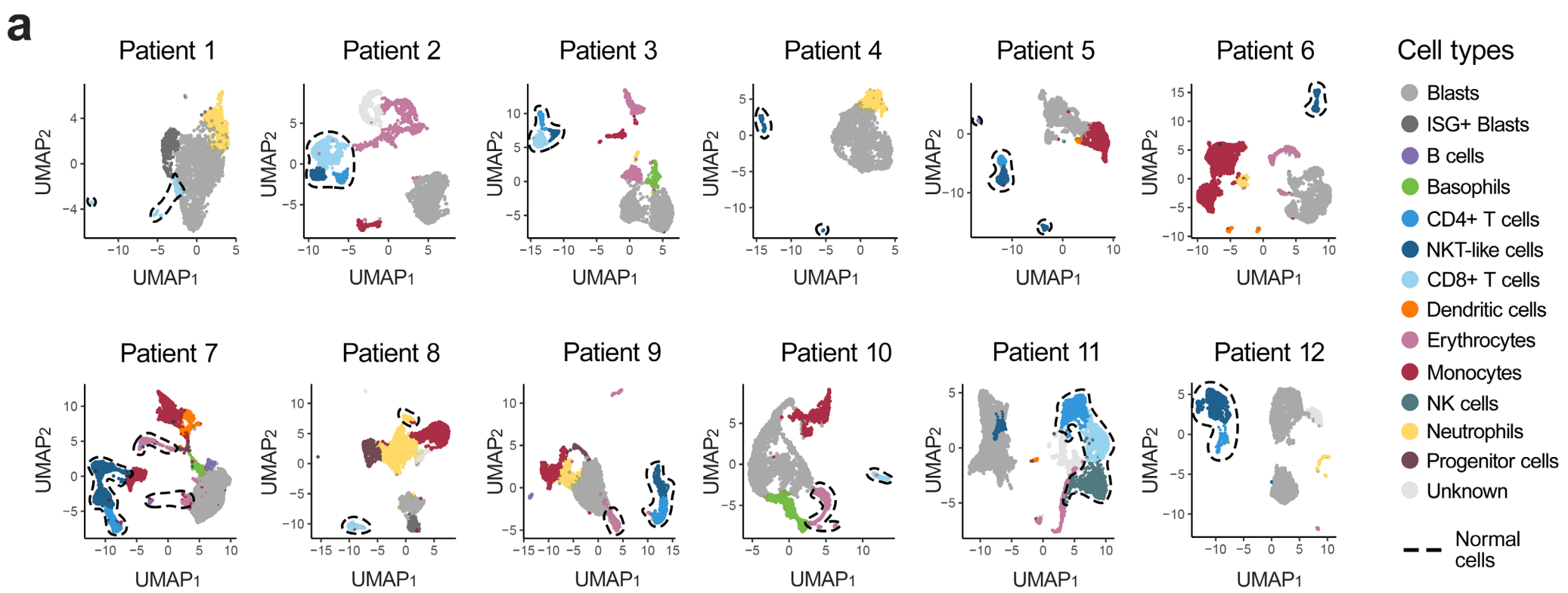

b
Up-regulated in
Subclone X
Normal cells
-log10(p-value)
log (FC)
Pre-trained machine-learning model
Subclone-specific differentially expressed genes
Pre-defined or user-provided drug information
Pre-trained LightGBM model
Subclone
Genes
Drug
ECFP, dose
Drug X
Drug Y
Drug Z
UMAP (dimension 2)
UMAP (dimension 1)


c
LINCS L1000 differential gene expression signatures
Genes
Drug A
Drug B
Drug Z
Cell line A
Cell line N
Drug structures represented as molecular fingerprints
Drug responses extracted from PharmacoDB and matched with LINCS L1000
% viability
high
low
Predictors
Outcome
PharmacoDB
Drug A
Cell viability (%)
Concentration
Concentration matched with LINCS L1000
Cell viability response at matched dose

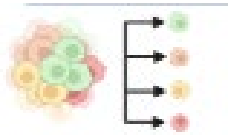
Heterogeneous cell type compositions across patients

Need for personalized treatment options

Cell type annotation – ScType + CopyKAT + SCEVAN

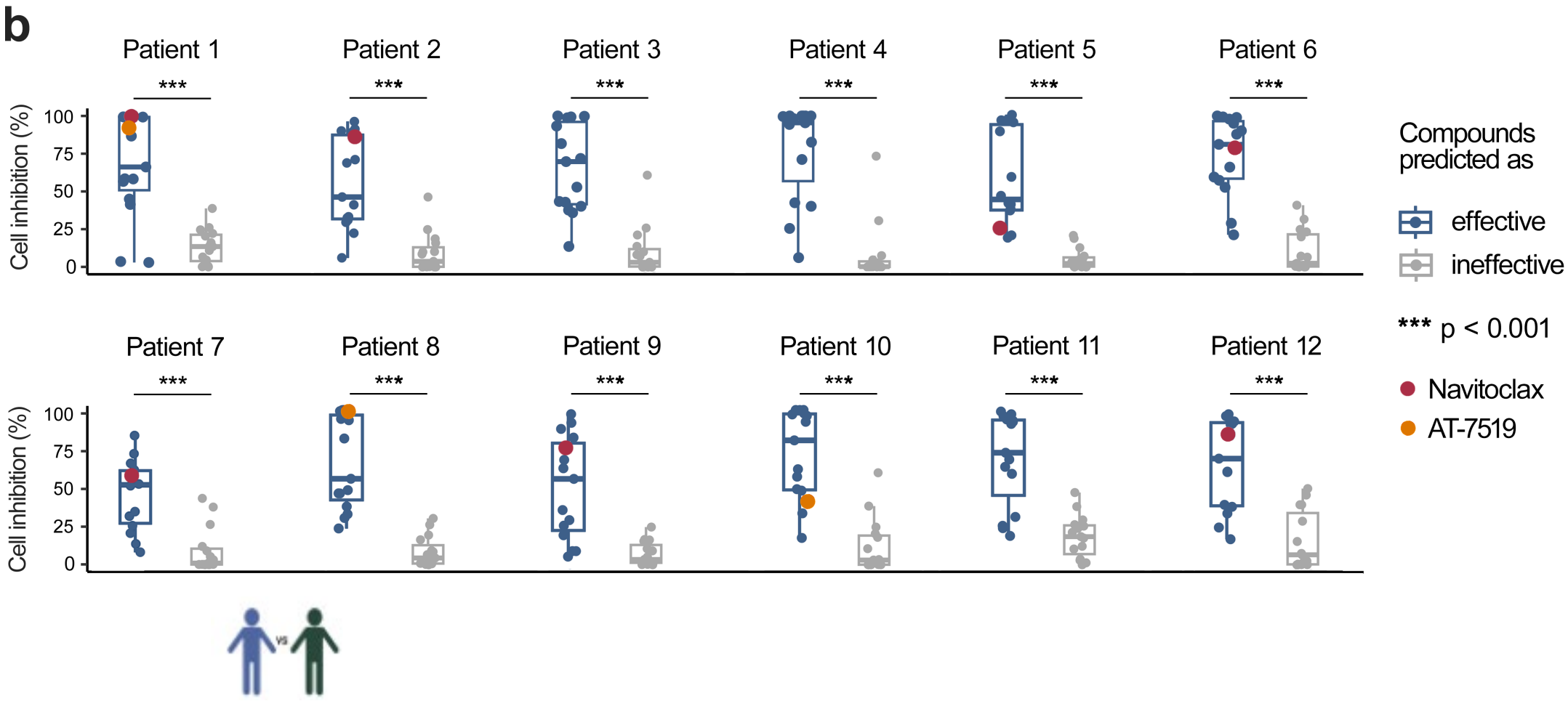


10x Genomics, FIMM single-cell core



Retrospective validation:

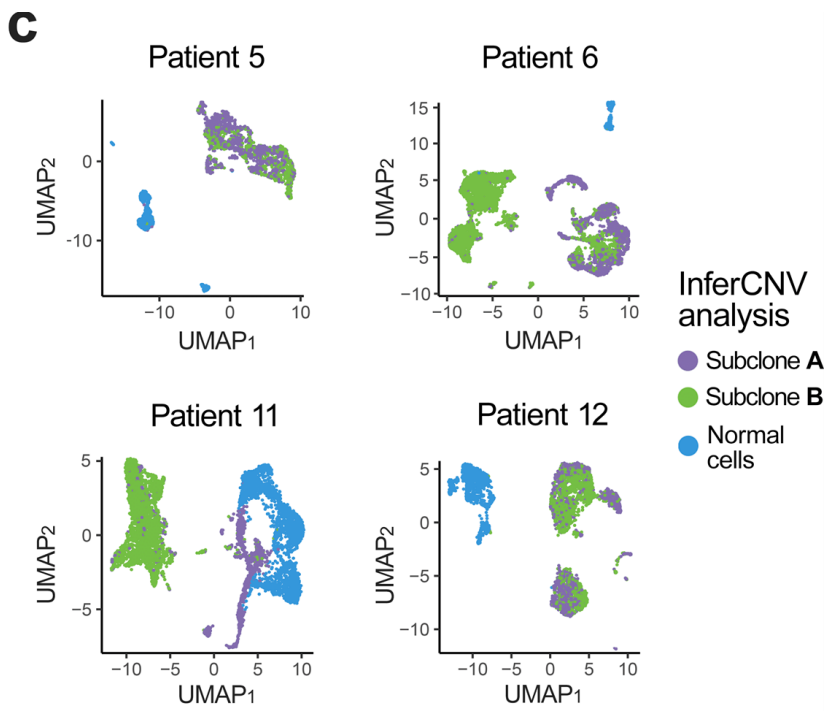
Bulk CTG drug response profiling confirms that the model predicts effective single-agent treatments



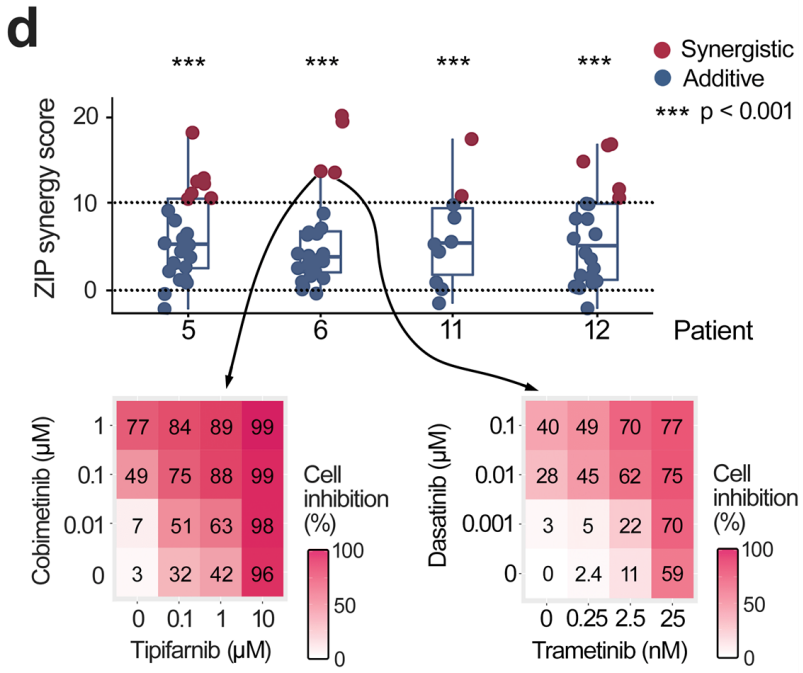
Prospective validation:

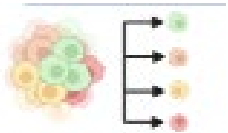
Patient- and clone-specific drug combination predictions in four AML patients

Identify subclones - InferCNV



Testing patient-specific combinations

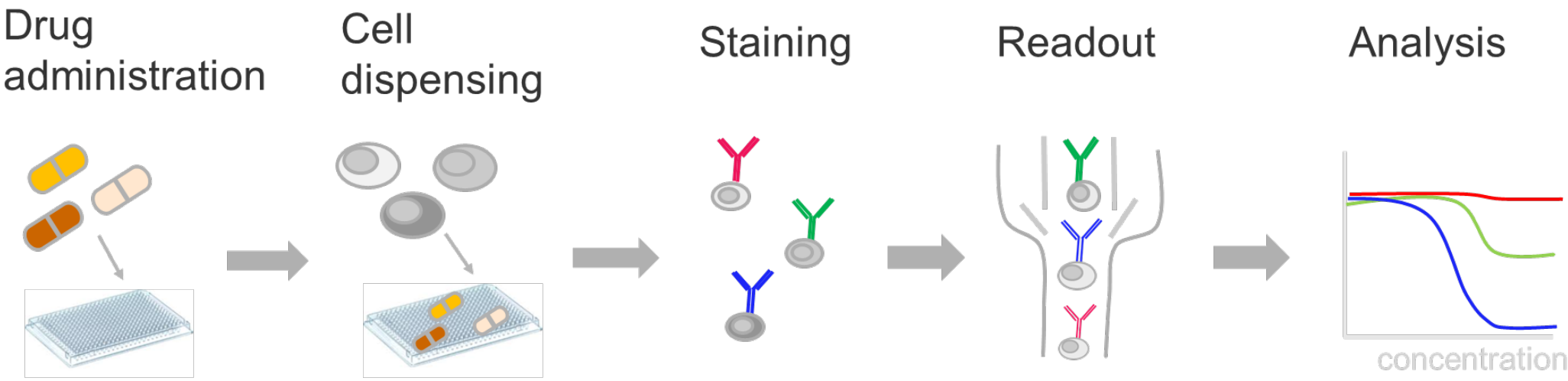




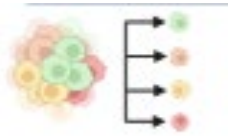
Flow cytometry cell population drug assay
Cancer cell-selective co-inhibition effects

Tanja Ruokoranta

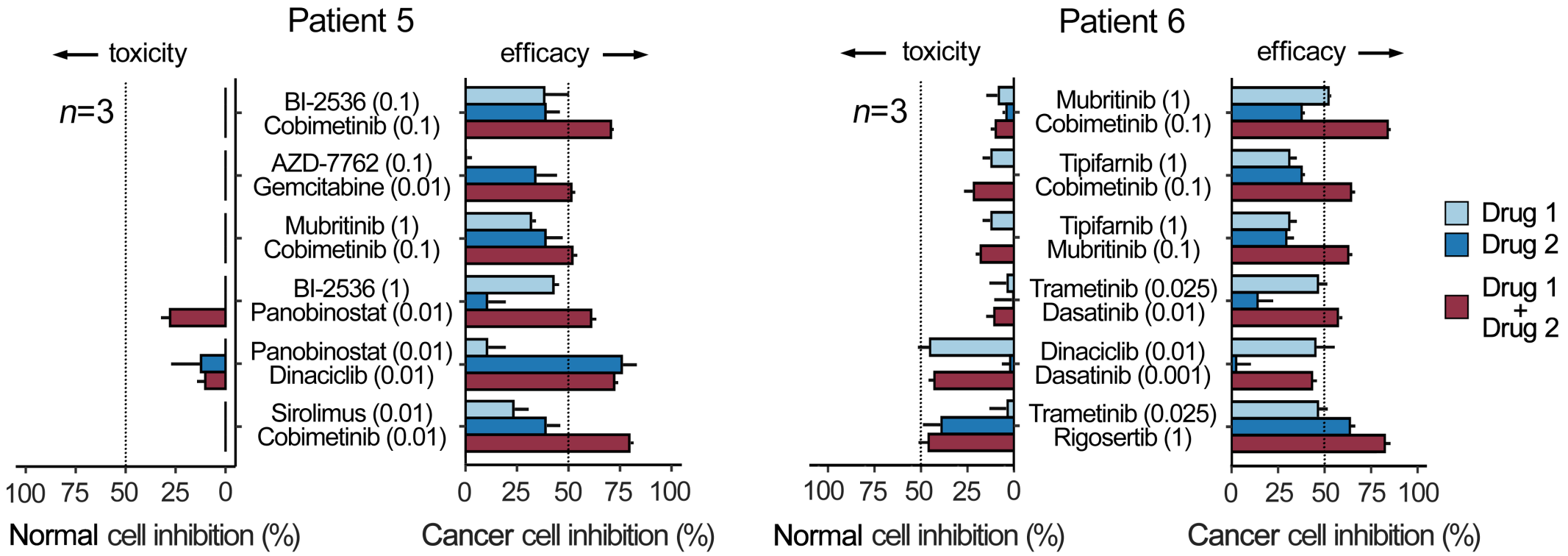
Heikki Kuusanmäki



blast cells vs. lymphoid cells

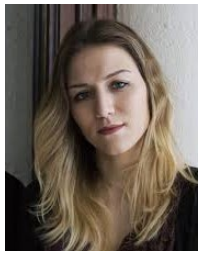


Trade-off between co-inhibition of healthy and cancer cells



Low toxicity: <50% relative co-inhibition of lymphoid cells (healthy cells)

Application to ovarian cancer patients Validation in patient-derived organoids



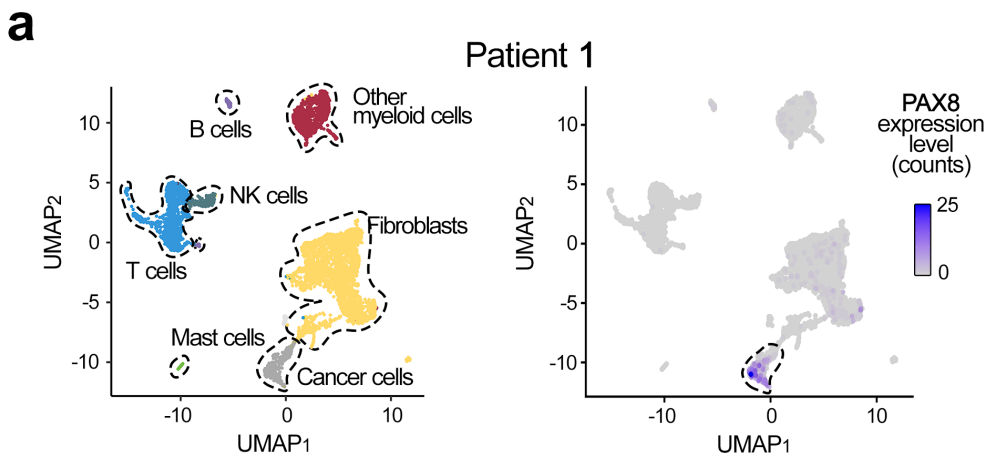

UNIVERSITY OF COPENHAGEN

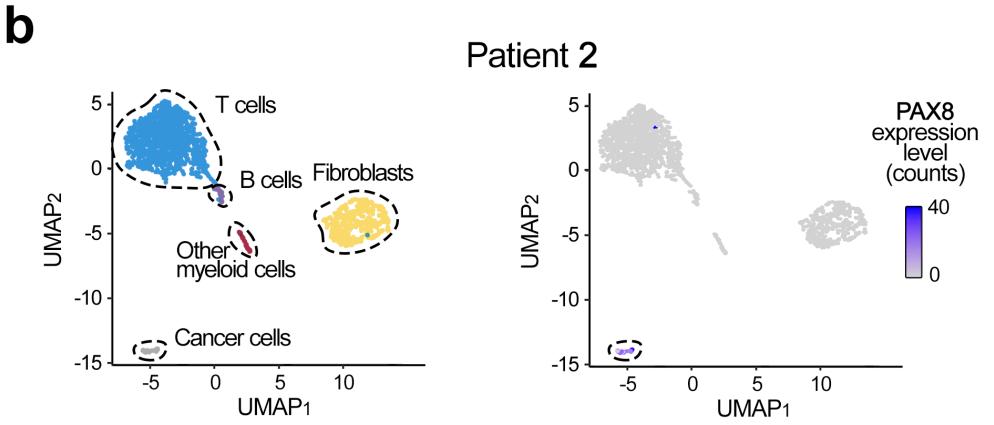
Kyriaki Driva

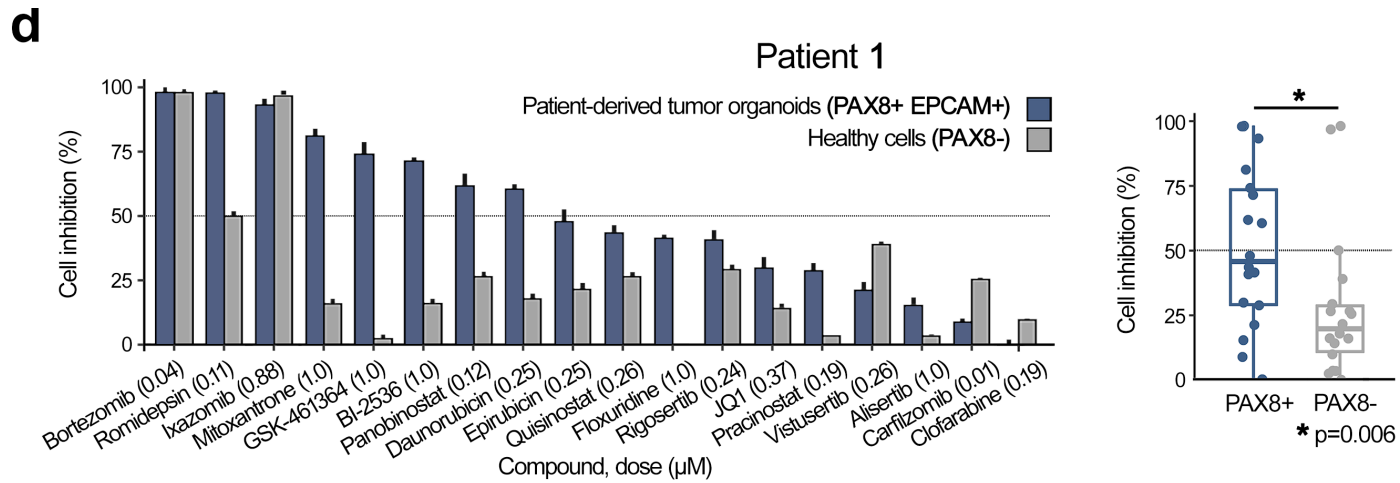
Daria Bulanova

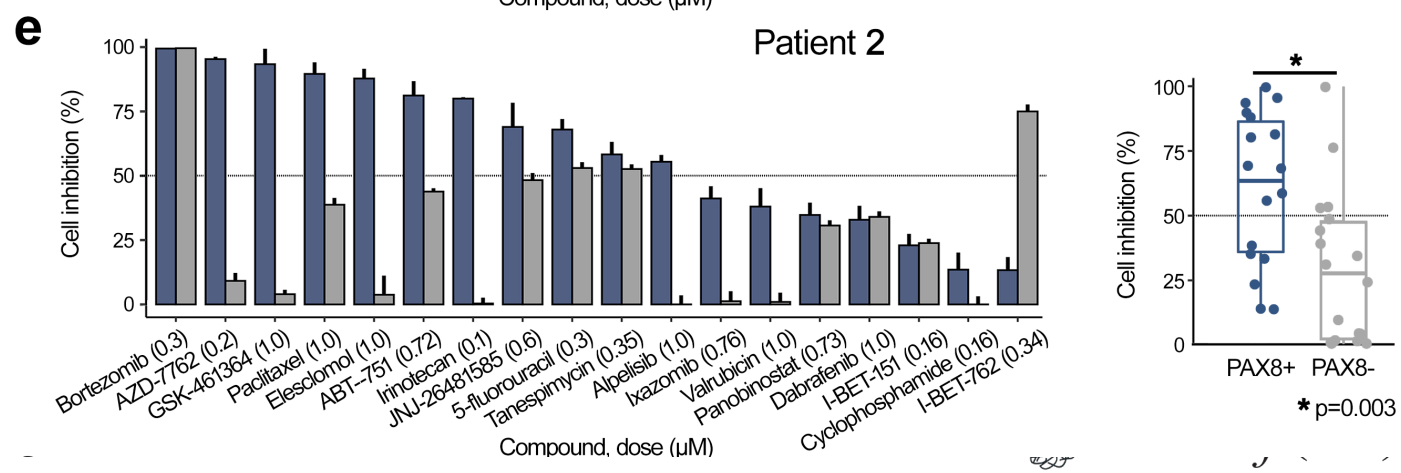
Wojciech Senkowski

Lidia M. Galceran









Conclusions

- Drug combination predictions using **only scRNA-seq** from patient samples
- Fast means for identifying **targeted treatments and doses** at subclone and patient level (diagnosis vs. relapse/refractory)
- Can be applied for tumours that are not easily amenable to *ex vivo* drug testing (most solid tumours)
- **96%** of the multi-targeting treatments were confirmed to exhibit selective synergy and **86%** low toxicity to normal cells
- Potential for improved therapeutic efficacy and safety
- Challenging to identify biomarkers from scRNA-seq data

Systematic approach to predict effective drug dose-combinations that minimize toxicity to healthy cells while selectively co-inhibit cancer cells

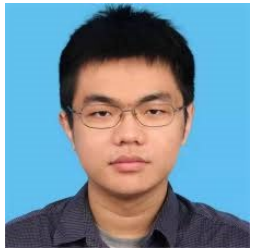
➡ **clinical response prediction as the next step (VenEx trial)**

ERA PerMed CLL-CLUE project

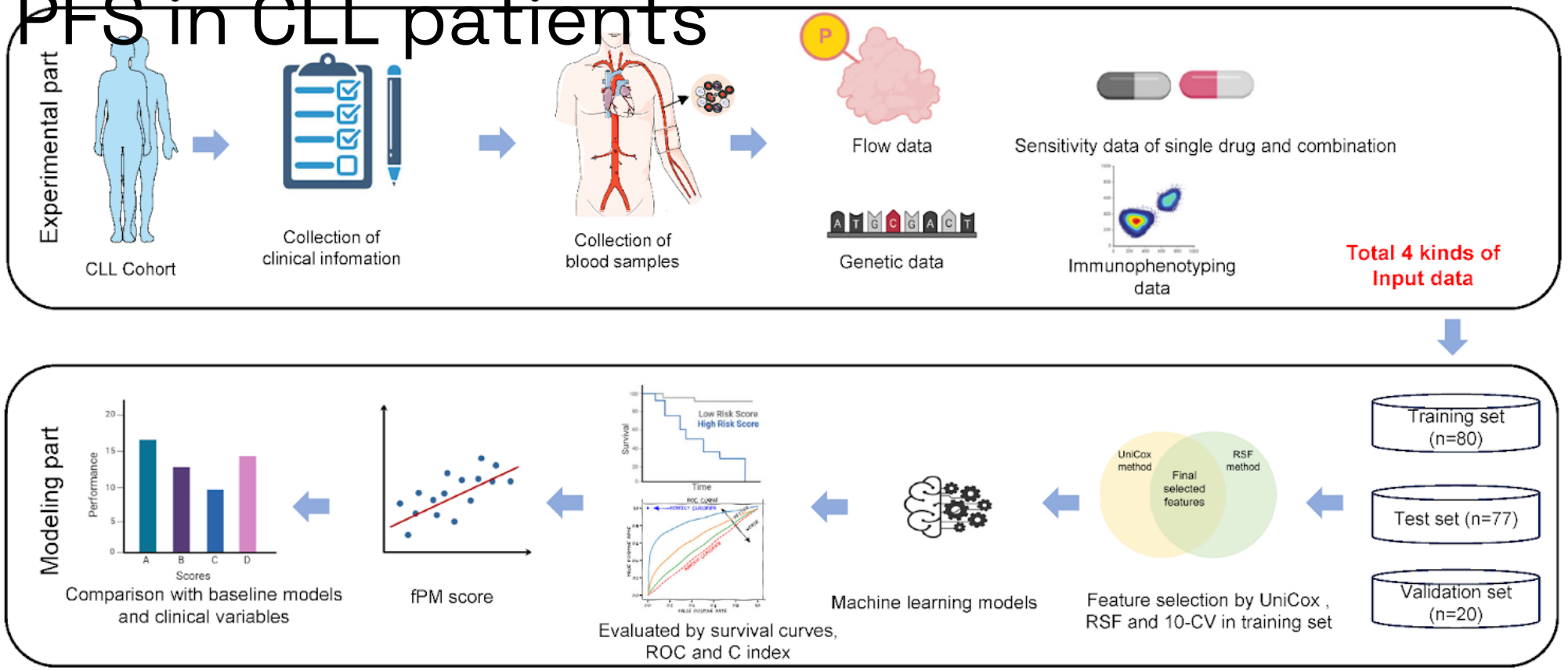
AI-based treatment decision support system

Rigshospitalet | UNIKLINIK KÖLN | Oslo University Hospital | University of Zurich[UZH] | syreon Research Romania | FIMM Institute for Molecular Medicine Finland, Nordic EMBL Partnership for Molecular Medicine

Functional precision medicine (fPM) score for progntostic predictions of PFS in CLL patients



Weikaixin Kong (FIMM)



Rigshospitalet → Oslo University Hospital → FIMM

Clinical expertise | Profiling technology | Machine learning

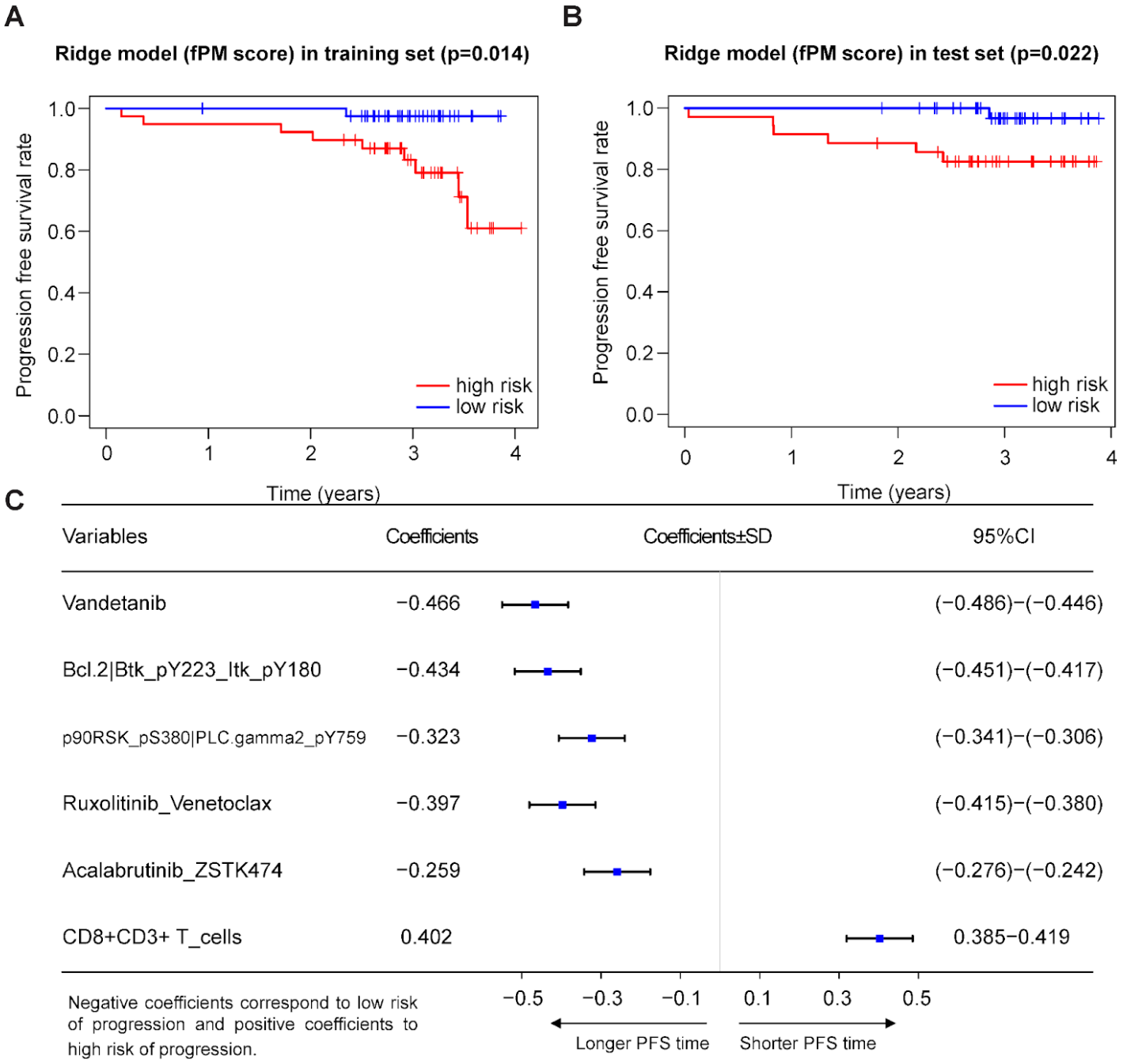


Figure 1. Survival curves of the fPM high and low-risk groups in (**A**) training cohort (n=80) and **(B**) test cohort (n=77). (**C**) The coefficients of the variables of the fPM score estimated in the training cohort. The median value of the fPM score in the training set (-0.01687) was used as the cutoff to separate between the hig- risk and the low-risk patient groups. Statistical significance of the PFS differences between the two groups was assessed with the log rank test.

Weikaixin Kong et al., EHA 2024
Sigrid Skånland, **S***f*(**PM**) poster

AML collaboration

Personalized Cancer Medicine

Caroline Heckman

Jonathan Knowles

Samuli Eldfors

Riikka Karjalainen

Jarno Kivioja

Ashwini Kumar

Heikki Kuusanmäki

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