Biological Insights From Plasma Proteomics: Uncovering Drivers of Treatment Response and Toxicity

Michal Harel, PhD | November 3, 2025

ISLB 2025 7th Annual Congress of Liquid Biopsy

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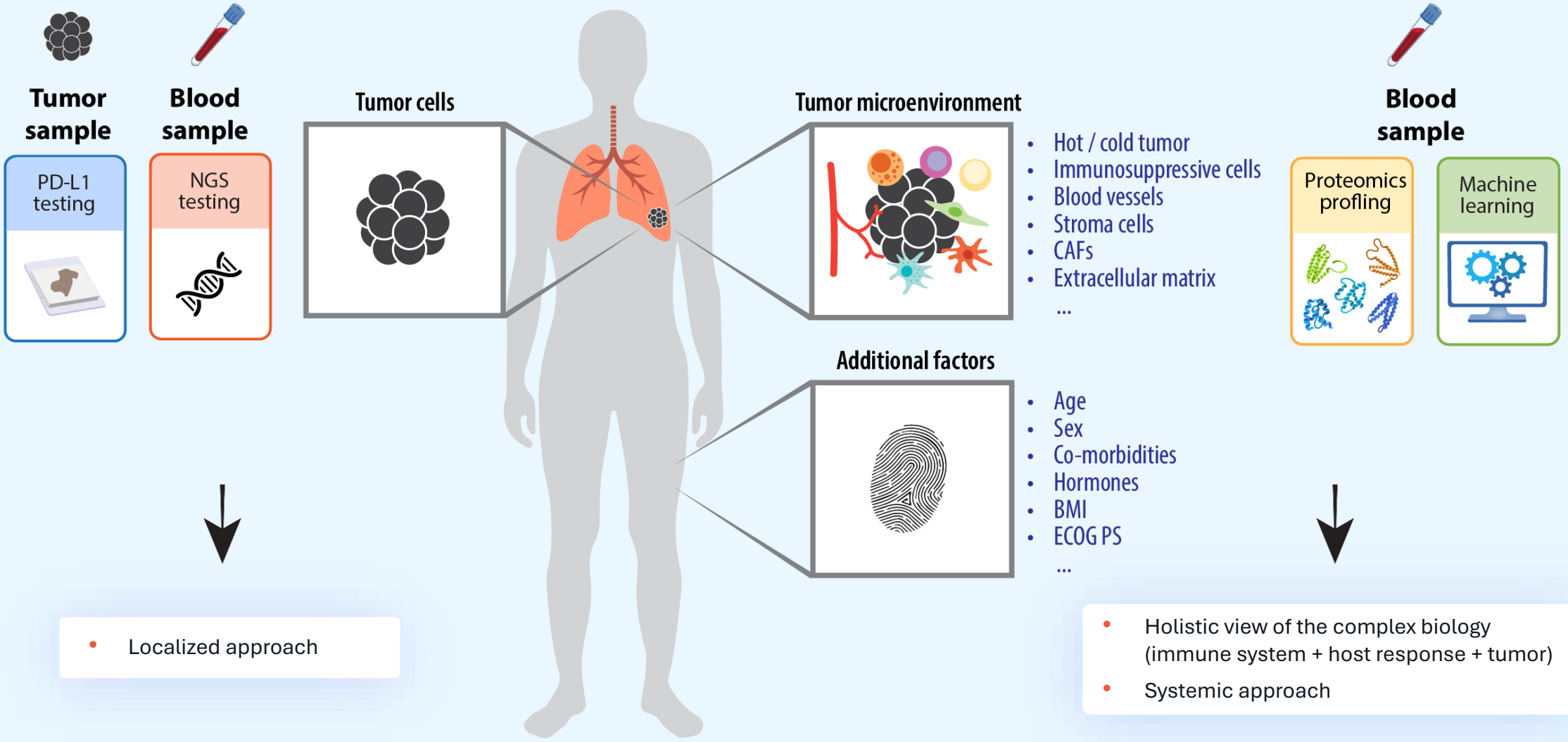
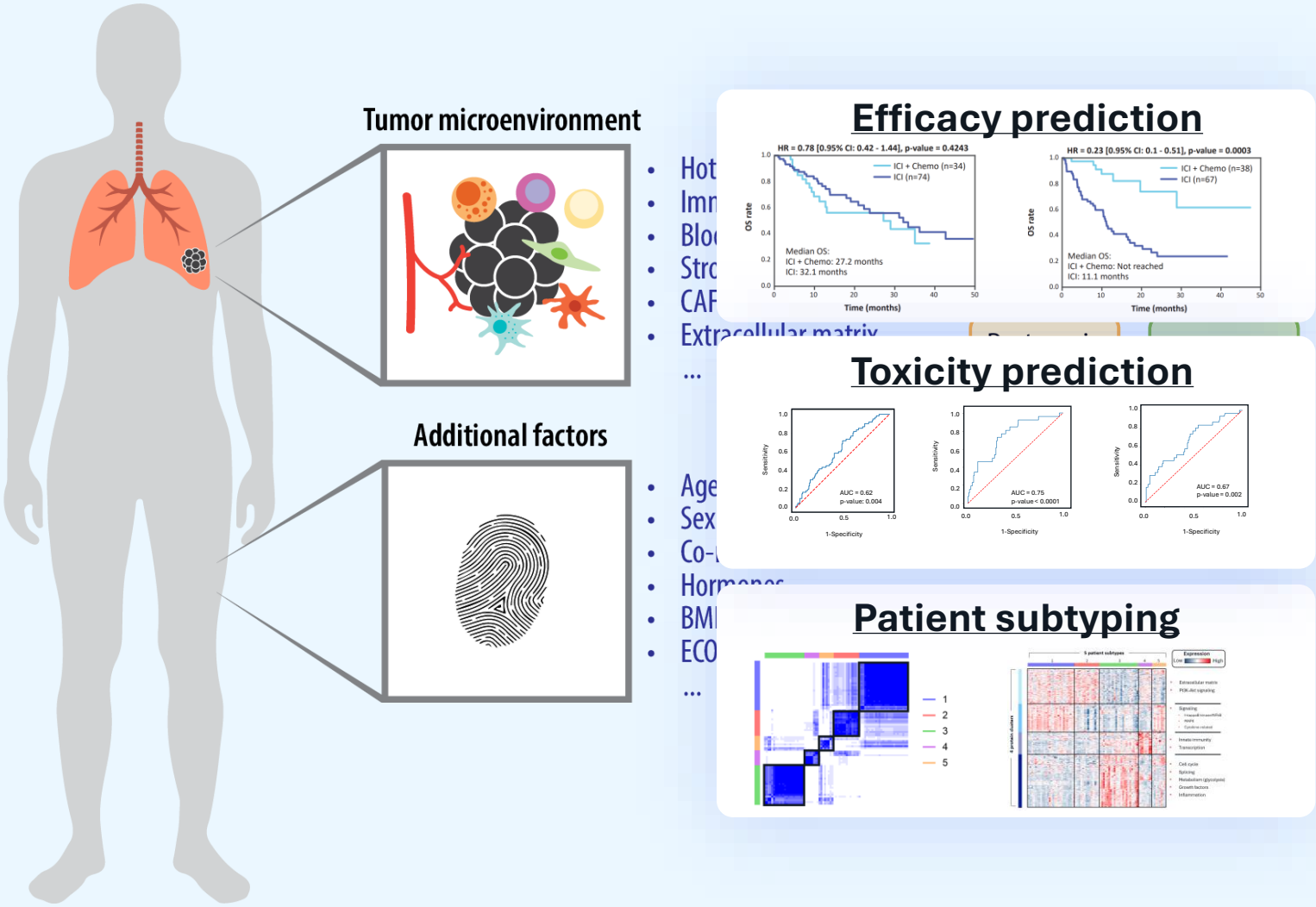
Personalized treatment calls for a multi-component biomarker



Personalized treatment calls for a multi-component biomarker



Plasma proteomics: What's in it for me?

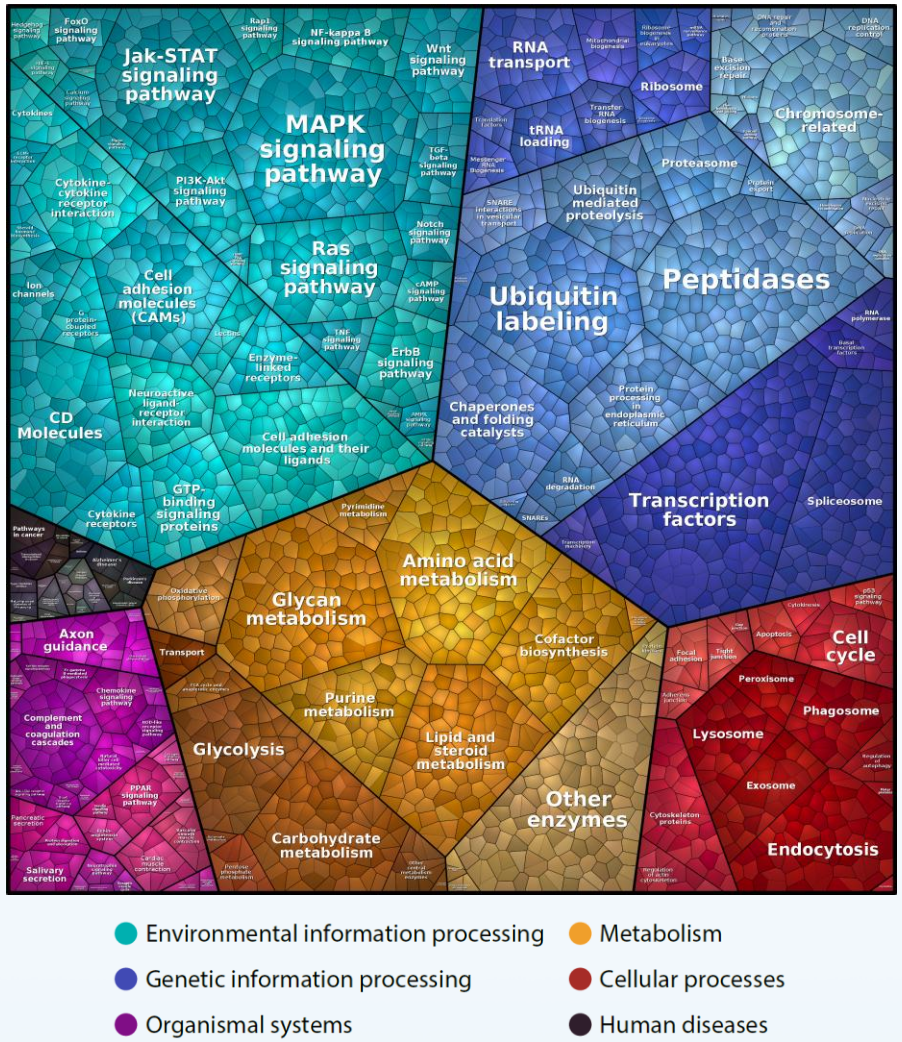
Proteomics holds the potential for deep coverage of multiple biological processes

Aptamer-based proteomic profiling

Examines expression levels of >7000 proteins per blood sample

Provides **deep exploration** of many biological processes

Coverage of aptamer-based proteomics

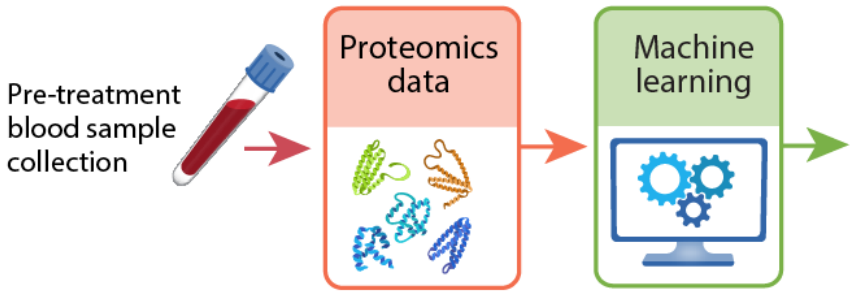


Treatment efficacy

PROphetNSCLC model, when combined with PD-L1, guides treatment for mNSCLC patients

PROPHETIC Trial (n=500)

Category	Parameter	# of patients
Sex	Male	302
	Female	198
ECOG-PS	0	191
	1	270
	2	37
	Unknown	2
PD-L1	High	199
	Low	141
	Negative	131
	Unknown	29
Histology	non-SqCC	370
	SqCC	101
	Unknown	29
Treatment type	ICI+Chemo	290
	ICI	210
Set	Development set	228
	Validation set	272

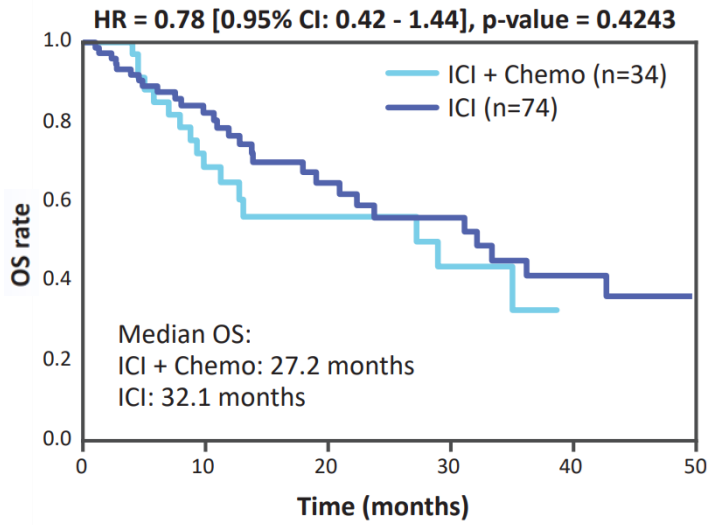


PROphetNSCLC result:

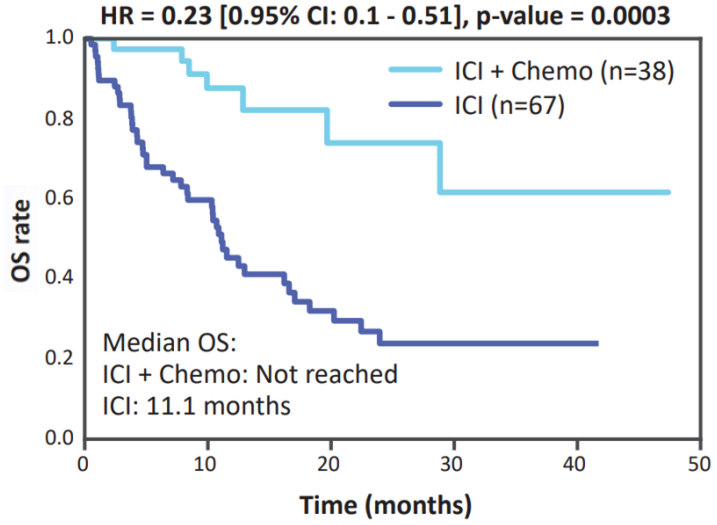
PROphet POSITIVE:
Good prognosis (mOS = 25.9 months)

PROphet NEGATIVE:
Poor prognosis (mOS = 10.8 months)

PROphet POSITIVE + PD-L1 ≥50%



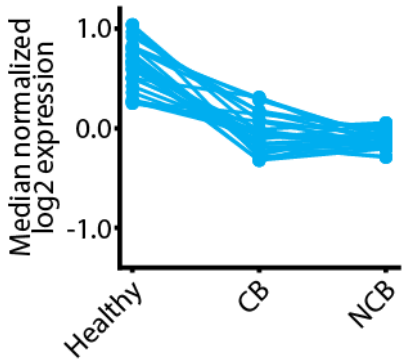
PROphet NEGATIVE + PD-L1 ≥50%



Christopoulos et al., JCO PO 2024

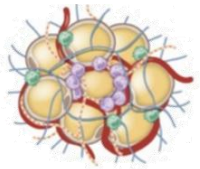
PROphetNSCLC model proteins display differential expression patterns between healthy, CB and NCB

Highest in healthy



Example:

LEP (Leptin)



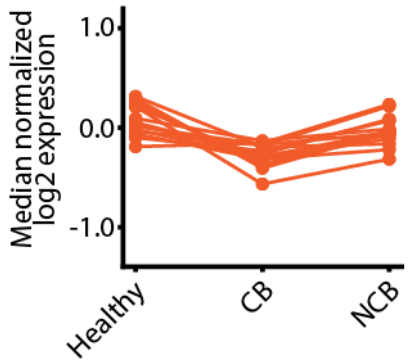
Adipose tissue

- Inflammatory cytokines
- Leptin
- Fatty acids

→

- **Immune modulation**
- **Increased ICIs activity**

Highest in healthy and NCB



Example:

CD39 (ENTPD1)

ATP/ADP

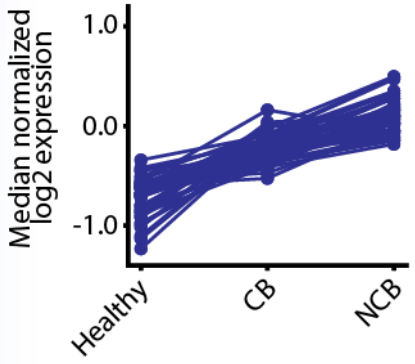
↓

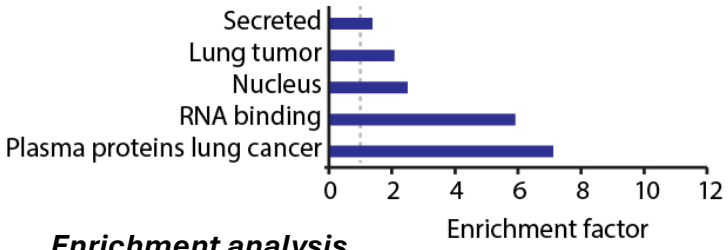
Adenosine

↓

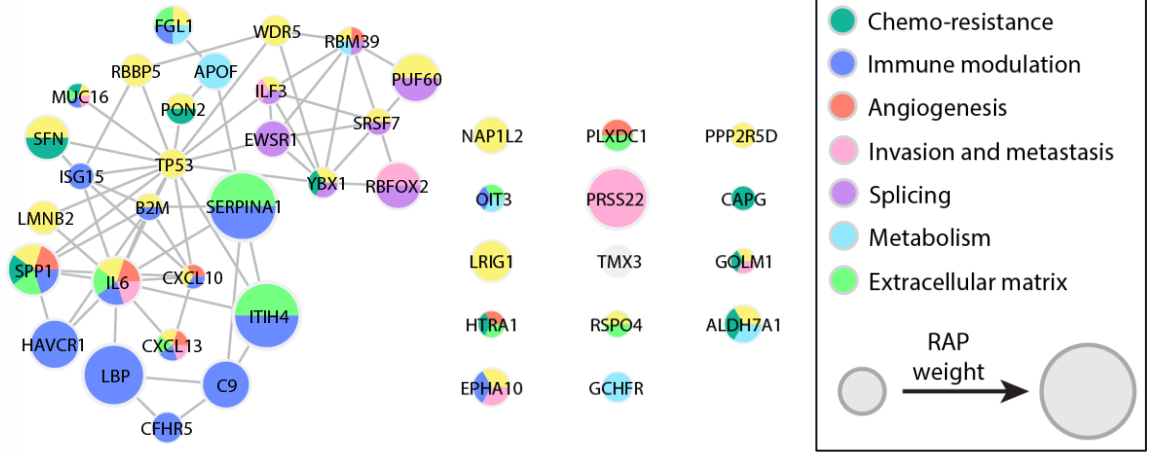
Immunosuppression

Highest in NCB





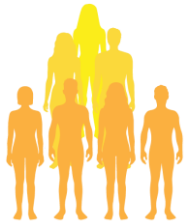
Enrichment analysis
Fisher's Exact test, FDR<0.1



CB = clinical benefit
NCB = no clinical benefit

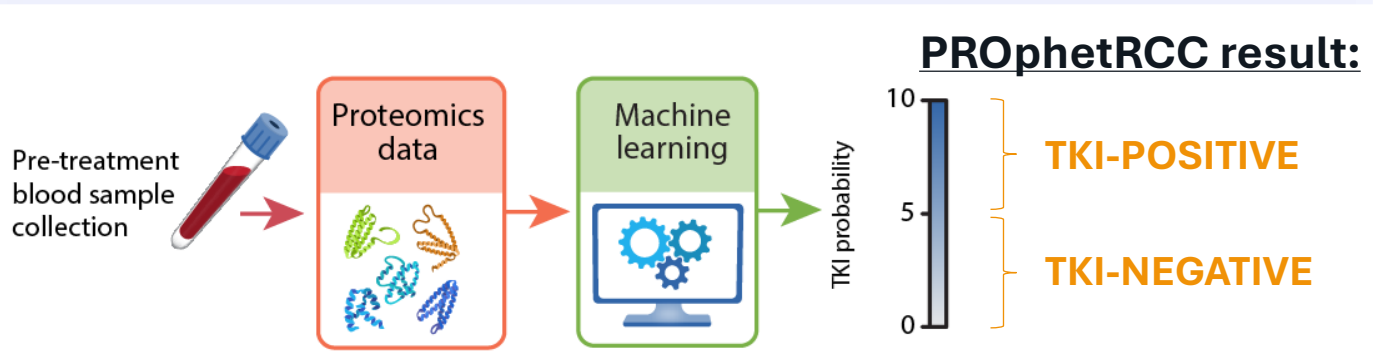
Harel et al., JITC 2025

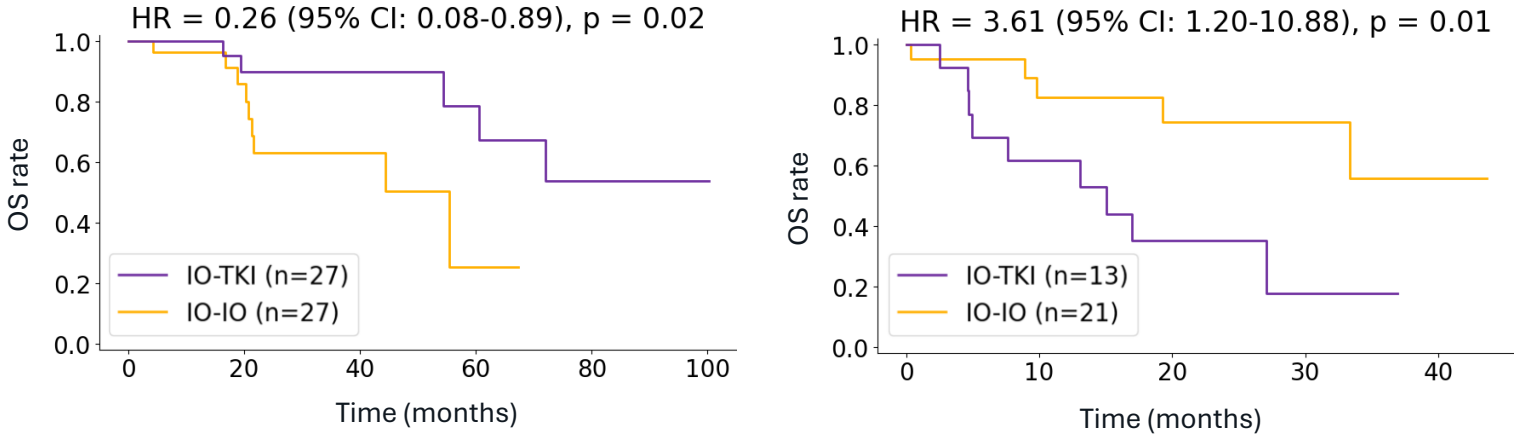
PROphetRCC informs treatment choice between IO–TKI and IO–IO in metastatic RCC



n=178

Patient Features		# of patients
Sex	Male	130
	Female	48
Treatment type	IO-IO	53
	IO mono	23
	TKI mono	62
	IO + TKI	40
Treatment line	First	158
	Advanced	20
Histology	Clear-cell	128
	Papillary	12
	Other	5
	Unknown	33
IMDC risk group	Favorable	24
	Intermediate	91
	Poor	30
	Unknown	33



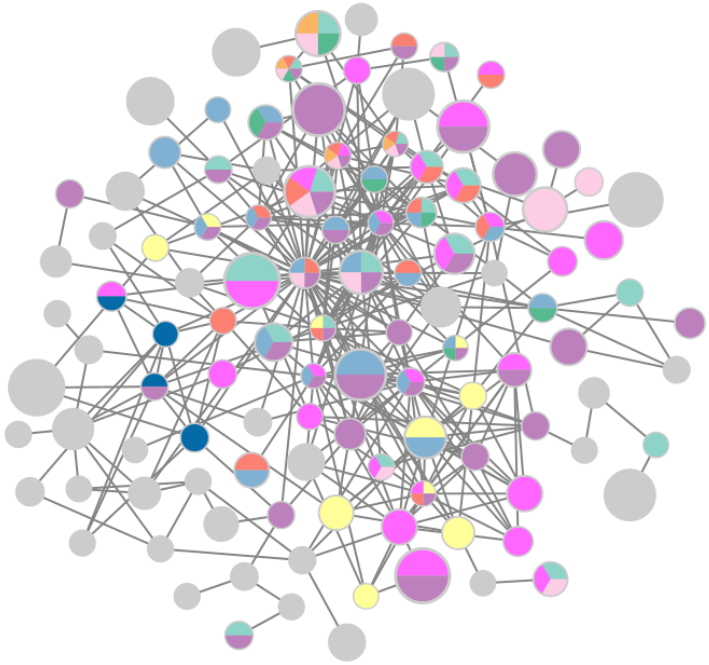


**** Results on validation set**

Steiner et al., In prep

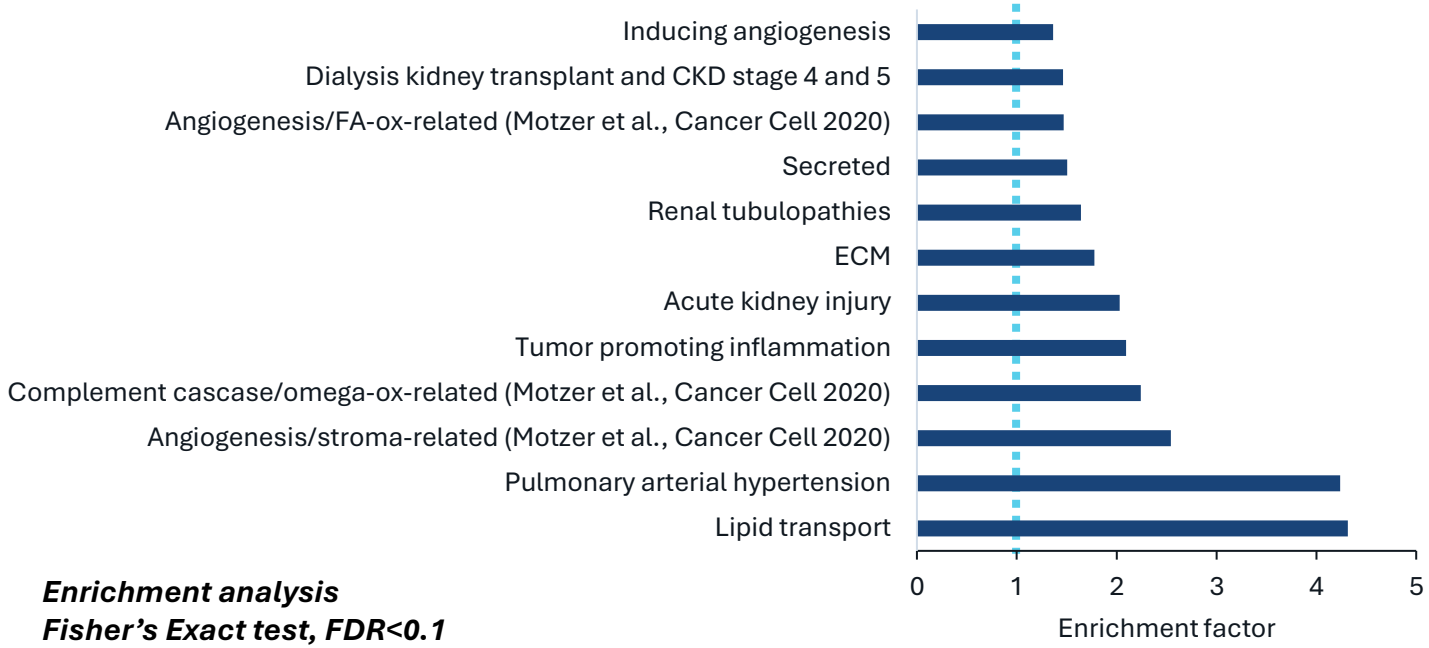
Multiple PROphetRCC proteins are kidney-associated or participate in angiogenic pathways

Functional network analysis



- RCC-related signatures
- PI3K-Akt signaling
- ERK1-ERK2 signaling
- VEGFA/PDGFA complex
- Angiogenesis
- Cholesterol / Lipid metabolism
- Oxidative stress response
- Inflammation
- Cell adhesion / Focal adhesion
- Extracellular matrix

Enrichment analysis



Enrichment analysis
Fisher's Exact test, FDR<0.1

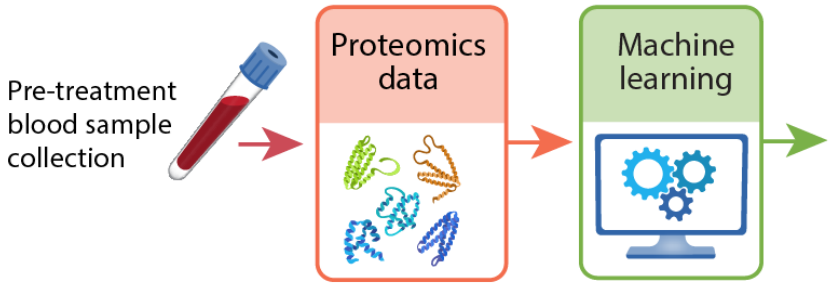
Steiner et al., In prep

PROphetSCLC identifies patients who benefit from ICI-chemo treatment

SCLC patients

n=79

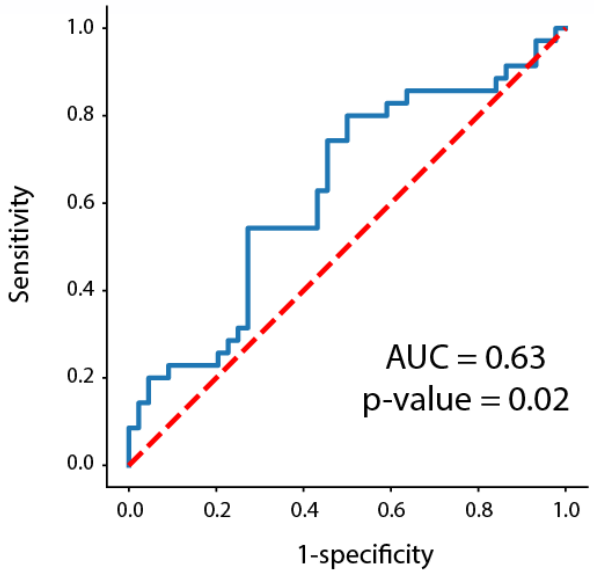
Category	Parameter	# of patients
Sex	Male	40
	Female	39
ECOG	0	24
	1	45
	2	8
	Unknown	2
Line of treatment	First	74
	Advanced	4
	Unknown	1
Treatment type	ICI+Chemo	77
	ICI combination	2
Clinical benefit	CB	35
	NCB	44
Age	Median (Q1, Q3)	65 (58, 70)

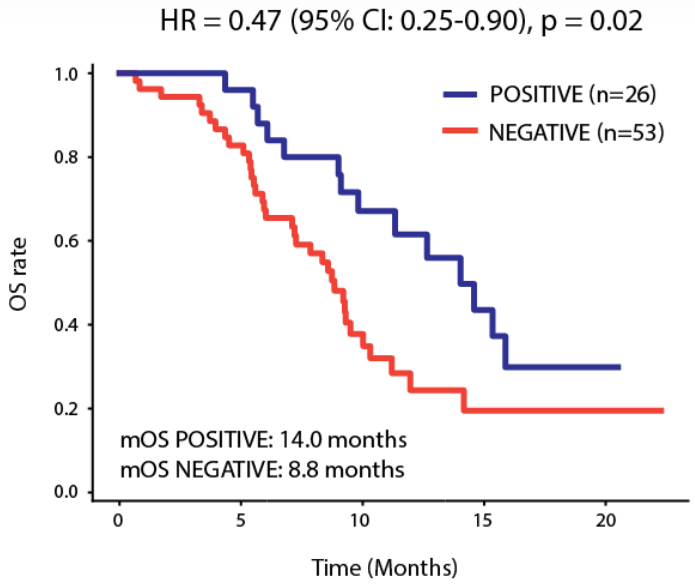


PROphetSCLC result:

PROphet POSITIVE:
Good prognosis (mOS = 14.0 months)

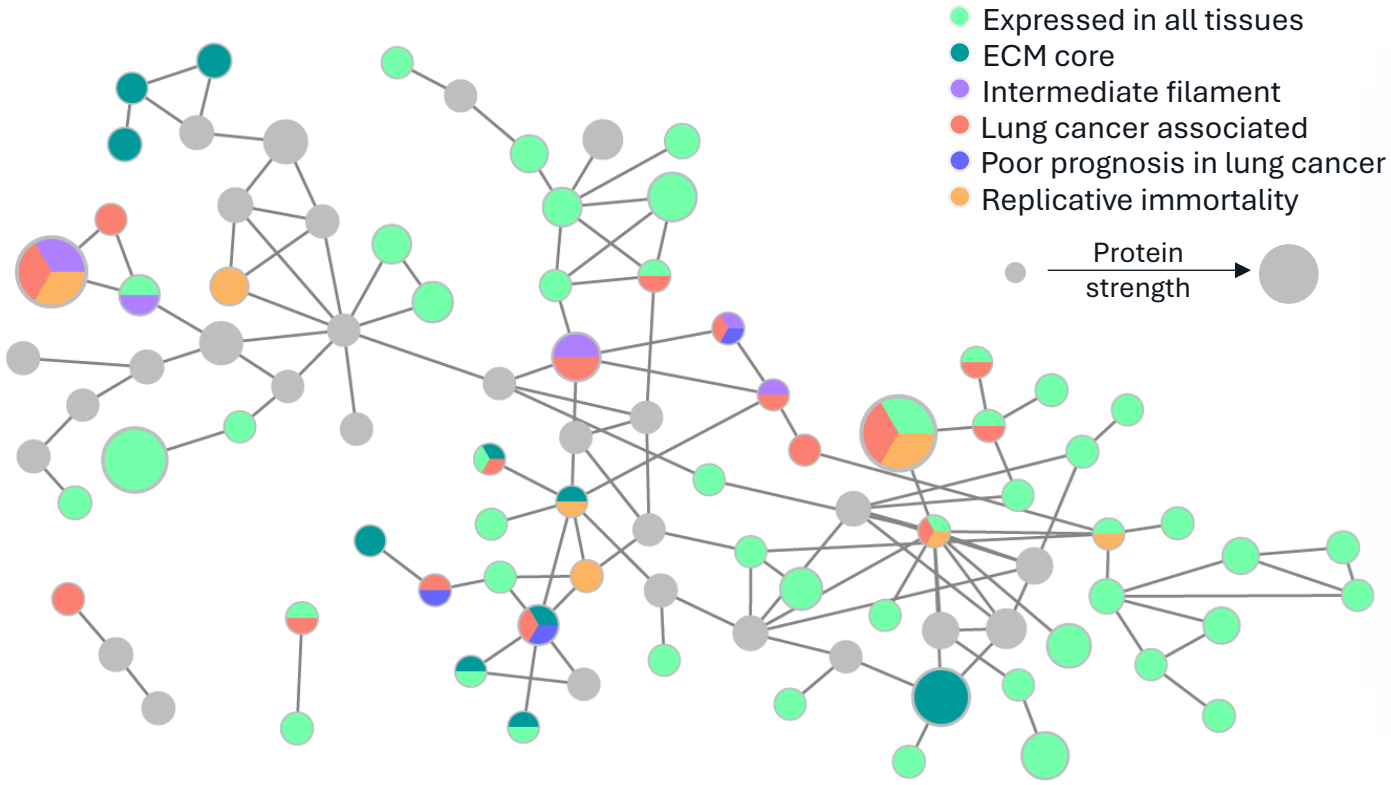
PROphet NEGATIVE:
Poor prognosis (mOS = 8.8 months)



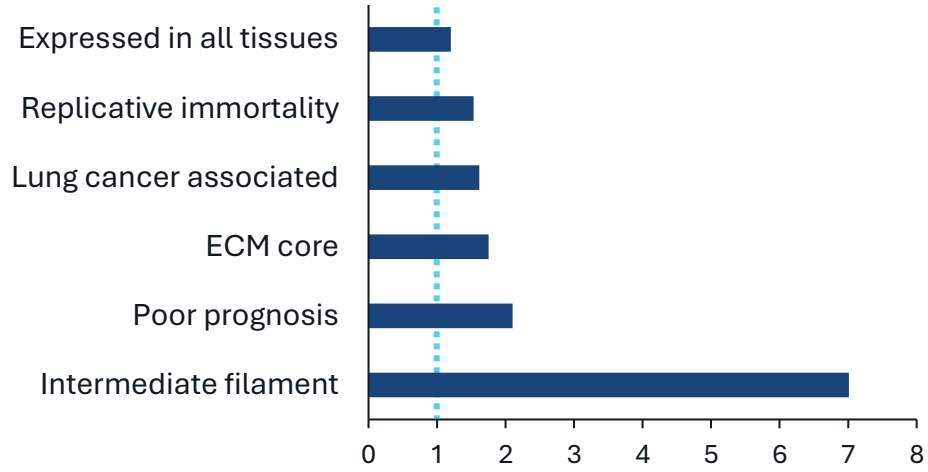


PROphetSCLC model proteins are associated with lung cancer and poor prognosis

Functional network analysis



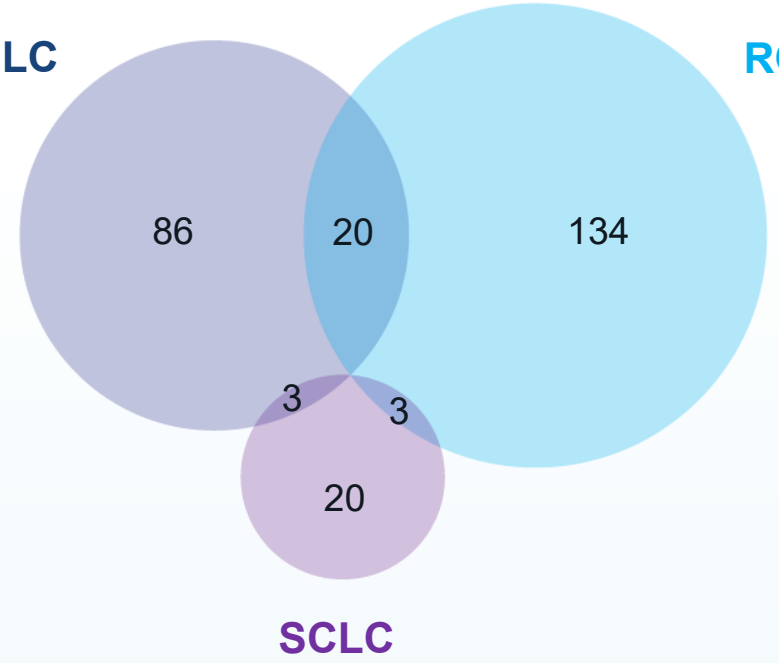
Enrichment analysis



Enrichment analysis
Fisher's Exact test, FDR<0.1

The three models of treatment efficacy are driven by distinct protein sets with differential biology

- Lung cancer-associated
- ICI resistance mechanisms



- Renal-related proteins
- Angiogenesis- related

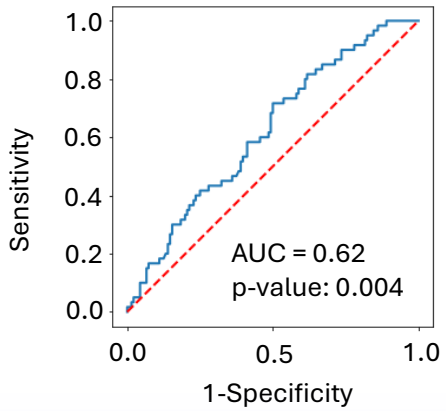
- Lung cancer-associated
- Poor prognosis in lung cancer

Toxicity prediction

Toxicity prediction: 3 different models

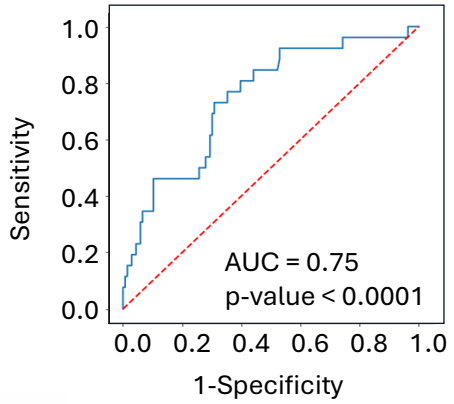
Severe irAE

Severe irAE:
grade ≥3 irAEs within the first 100 days leading to treatment discontinuation



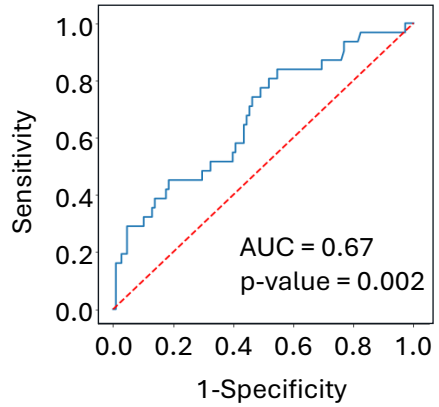
Rash-irAE

Rash irAE
Any grade rash that was defined as irAE

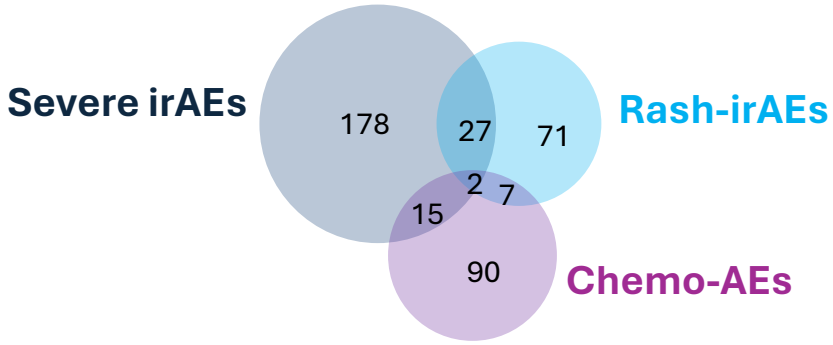


Chemo-AE

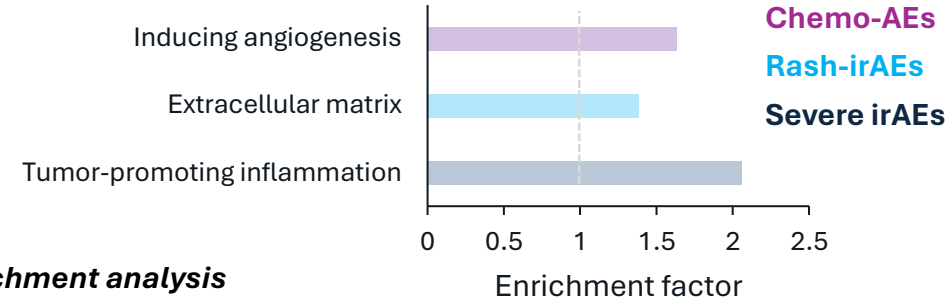
Chemo AE
Studied on a cohort of chemo only patients



3 distinct models

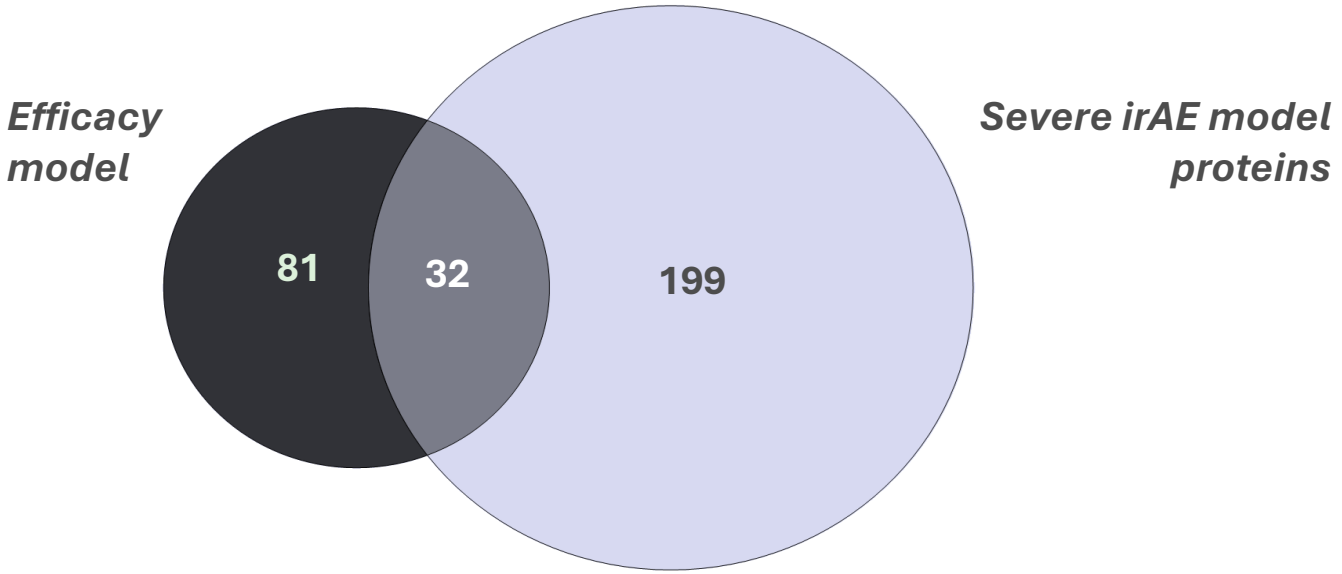


Main biological signal in each model



Enrichment analysis
Fisher's Exact test, FDR<0.1

Efficacy and toxicity models in NSCLC are distinct



Minimal overlap between proteins associated with clinical benefit and irAEs

Patient subtyping

SCLC patient subtyping using plasma proteomics identifies 5 subtypes

n=79

Category	Parameter	# of patients
Sex	Male	40
	Female	39
ECOG	0	24
	1	45
	2	8
	Unknown	2
Line of treatment	First	74
	Advanced	4
	Unknown	1
Treatment type	ICI+Chemo	77
	ICI combination	2
Clinical benefit	CB	35
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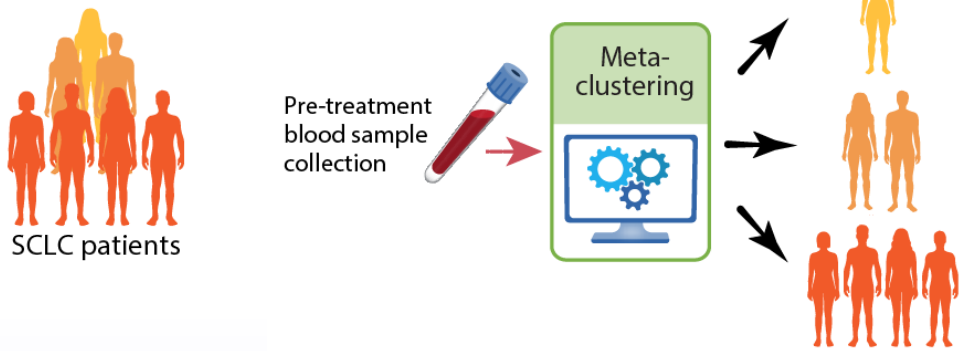
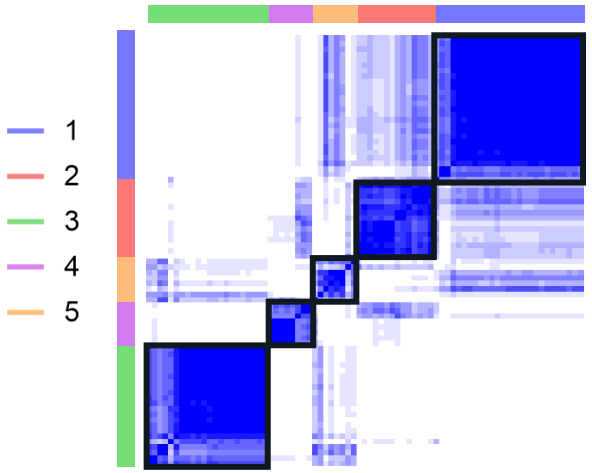
Age	Median (Q1, Q3)	65 (58, 70)

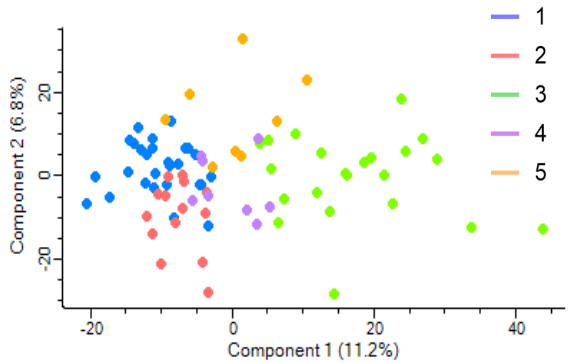


Subtype identification



Subtype	%
1	34.2
2	17.7
3	27.9
4	10.1
5	10.1

PCA



Linking subtypes to therapeutic vulnerabilities

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n=79

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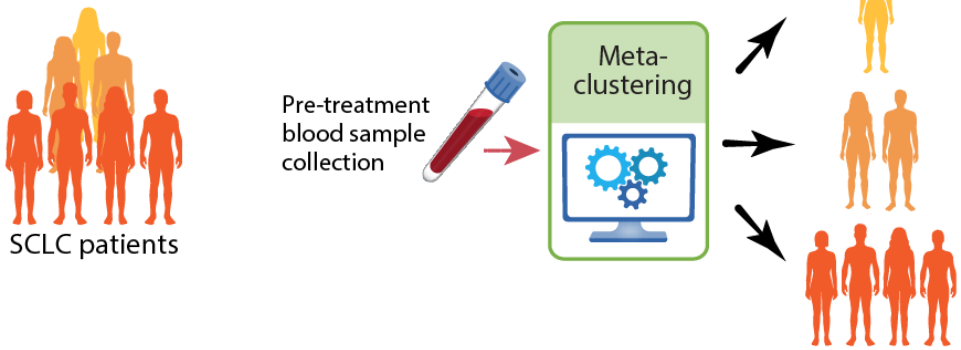
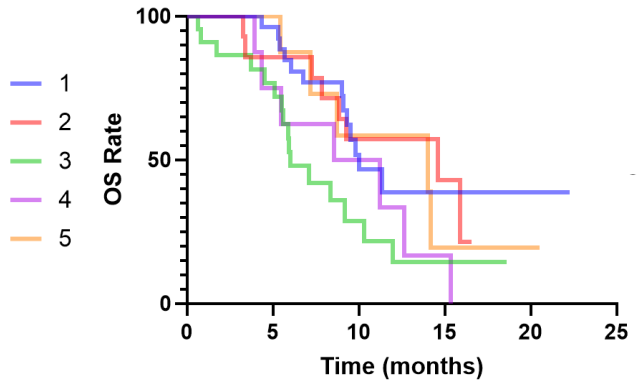


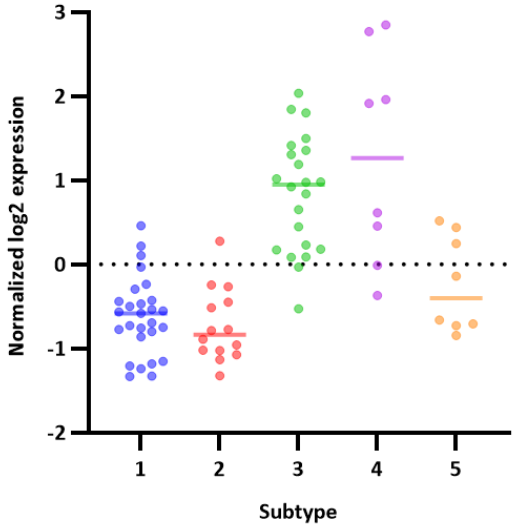
ICI-chemo treatment:



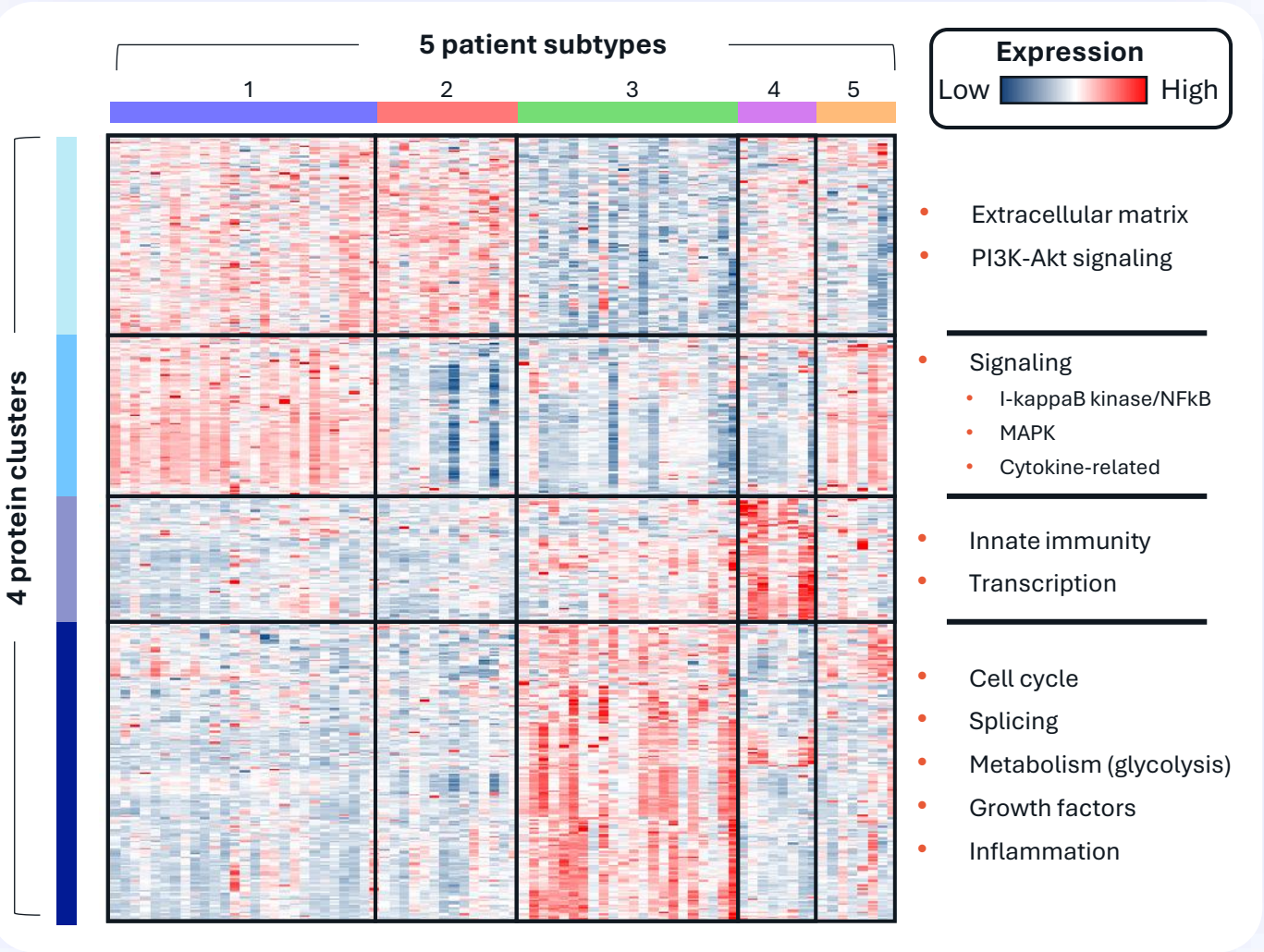
Subtype	mOS
1	10.03
2	14.60
3	6.02
4	9.90
5	14.04

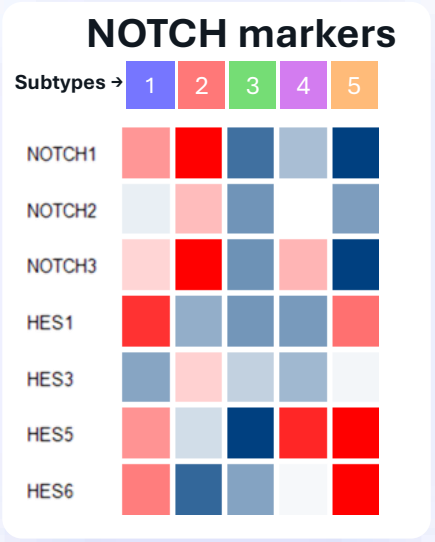
Comparison	P-value	HR (95% CI)
S1 vs S3	0.02	0.42 (0.19 to 0.90)
S2 vs S3	0.04	0.44 (0.20 to 0.98)

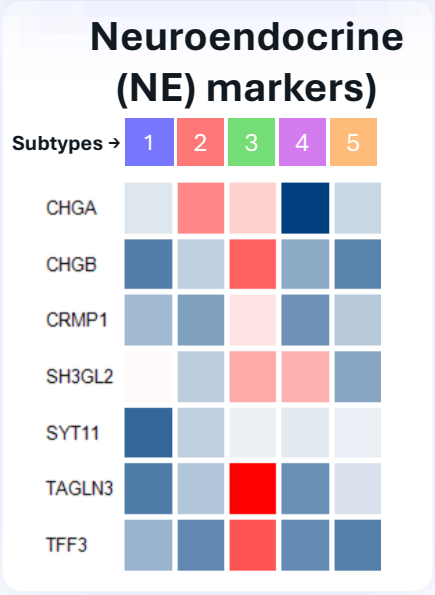
BCL2 levels:



The five subtypes display differential biological processes and signal







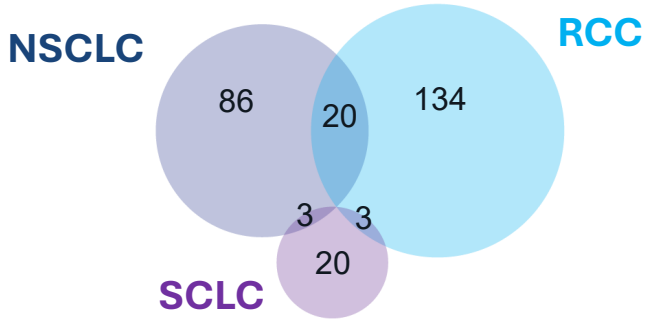
- Comparing the proteins that define each subtype reveals **distinct biological** differences between them
- **Subtype 3** shows stronger **NE signals** and is more similar to SCLC-A than the other subtypes
- **Subtypes 1-2 and 5** have stronger **NOTCH-related** signal

DEPs were identified using ANOVA FDR<0.01
469 DEPs

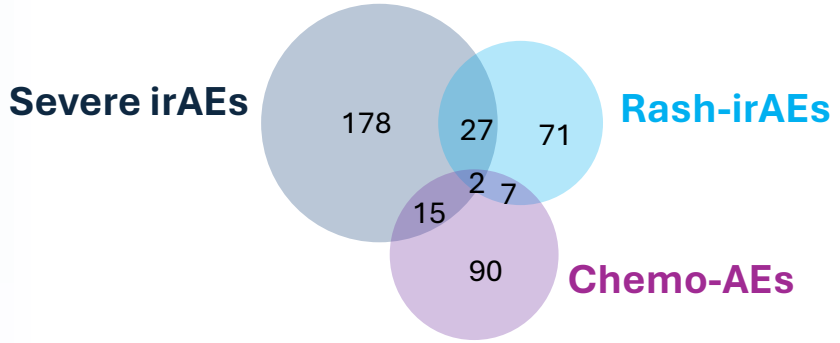
Summary

Plasma proteomics offers a rich foundation for developing biologically informed models across diverse clinical applications

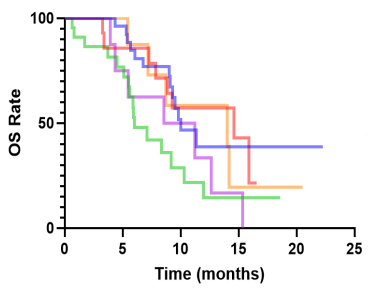
Treatment efficacy

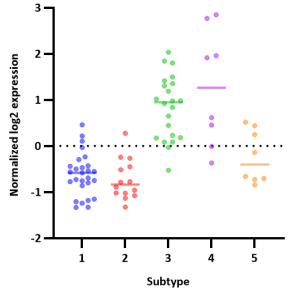


Treatment toxicity



Patient subtyping





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