How networks could be useful?
Simulation-first drug discovery in oncology

Daniel Veres MD PhD [1,2]

1) Turbine Ltd.
2) Semmelweis University

1. Who are we?

2. Why do we need Turbine?

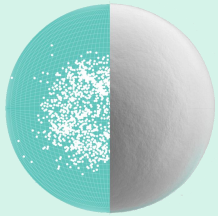
3. Overview of the technology

4. Simulation benefit in drug discovery

5. Summary and outlook

Turbine | a snapshot

Proprietary technology taking precision oncology beyond CRISPR



Simulated Cell™

- Cell behaviour simulation technology tackling high unmet need with the potential of enhanced clinical success
- Focus on oncology
- Patent-protected
- Based on 10+ years of research

Building pipeline targeting massive unmet oncology need for 1.5 years

4 targets tackling PARPi resistance

2 Hit finding phase

1 Initial patent filed

Predictions validated in clinical trials

BAYER

Top US Pharma

Top EU Pharma

5 of our predictions are investigated in Phase 1 – 3 clinical trials

Backed by tech/life sciences VCs

- €10M raised to date

Accel · BAYER · [XTX] MARKETS · Delin ventures

A team of ~50 combining molecular biology with engineering

- AI Engineers
- Data scientists
- Software developers
- Molecular & translational biologists
- Medchem experts

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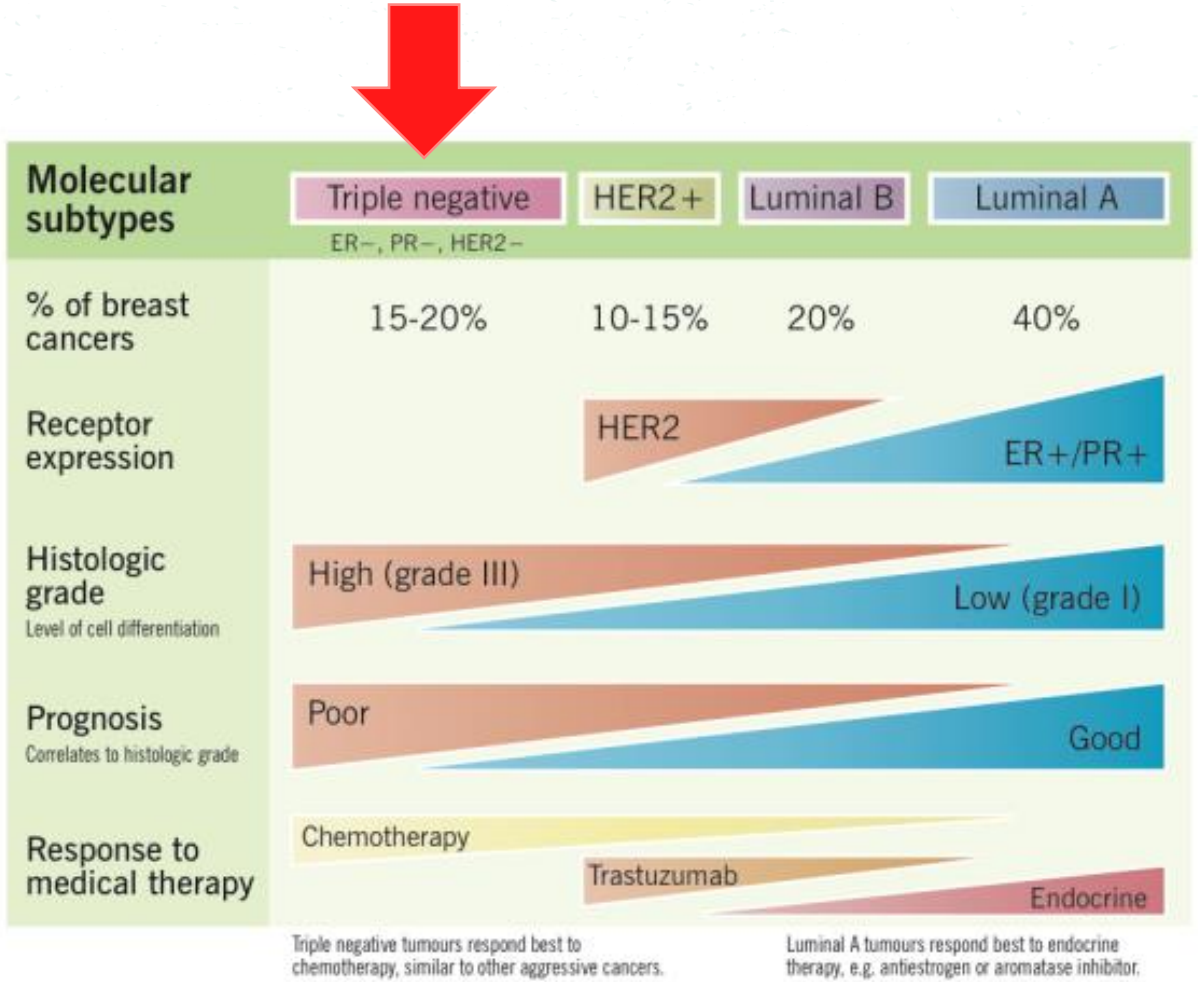
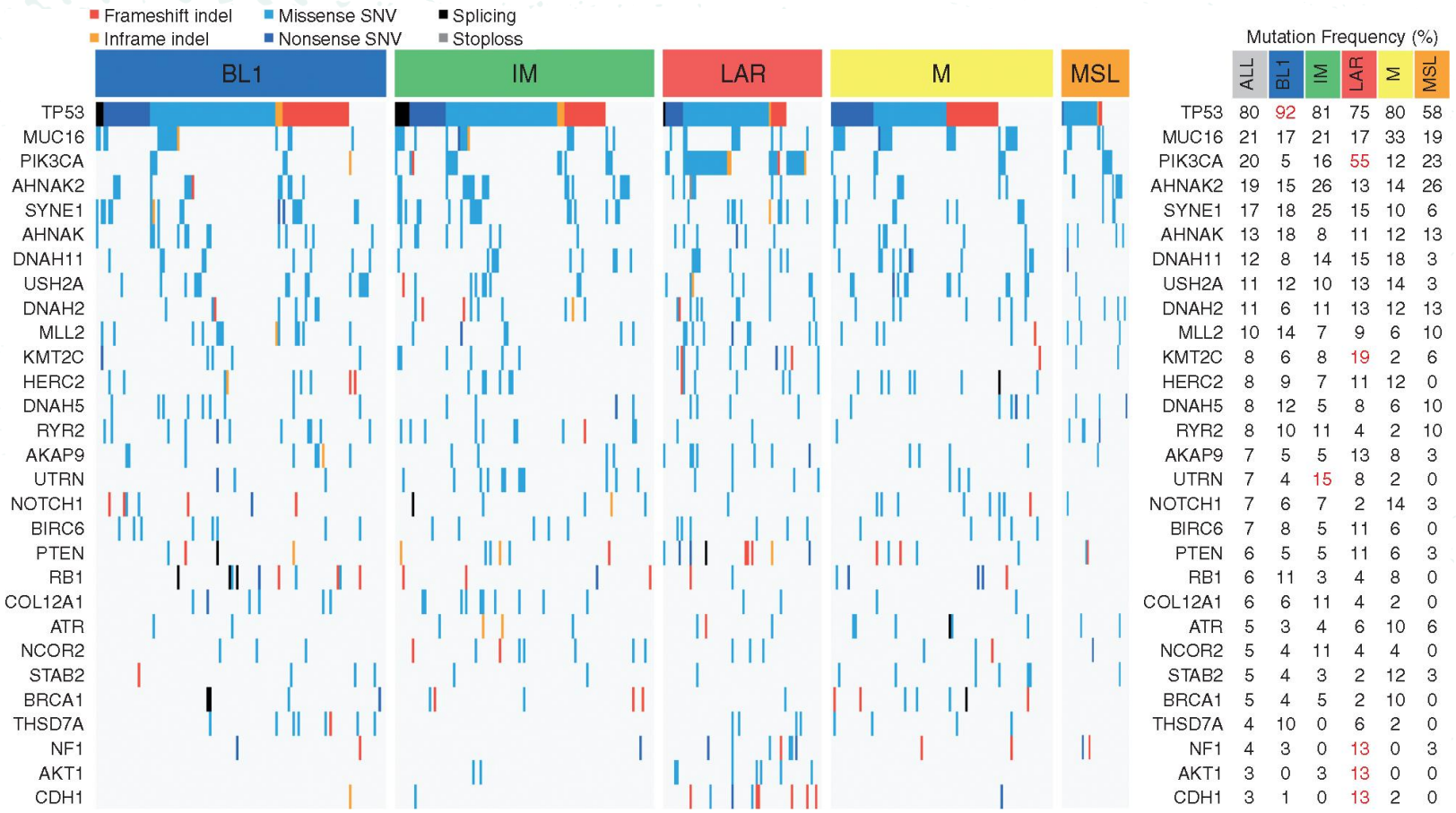
Advancements in molecular diagnostics leads to the fragmentation of cancer indications

Histological subtypes	Ductal	Lobular
Preinvasive cancer 25% Cells limited to basement membrane	Ductal carcinoma in situ (DCIS) 80% May spread through ducts and distort duct architecture 1% progress to invasive cancer per year Usually unilateral	Lobular carcinoma in situ (LCIS) 20% Does not distort duct architecture Same genetic abnormality as ILC – E-cahderin loss 1% progress per year Can be bilateral
Invasive cancer 75% Extension beyond the basement membrane	Invasive ductal carcinoma (IDC) 79% Usually from DCIS precursor Cause fibrous response, producing a palpable mass on examination Metastasis through lymphatics and blood	Invasive lobular carcinoma (ILC) 10% Usually from LCIS precursor Minimal fibrous response, presents less often with palpable mass Metastasis through abdominal viscera to GI, ovaries, uterus Almost always ER+

Curr Treat Options Oncol. 2000 Aug;1(3):199-209.
Clin Transl Oncol. 2008 Dec;10(12):777-85.
Nat Clin Pract Oncol. 2007 Sep;4(9):516-25.
Robbins 8E



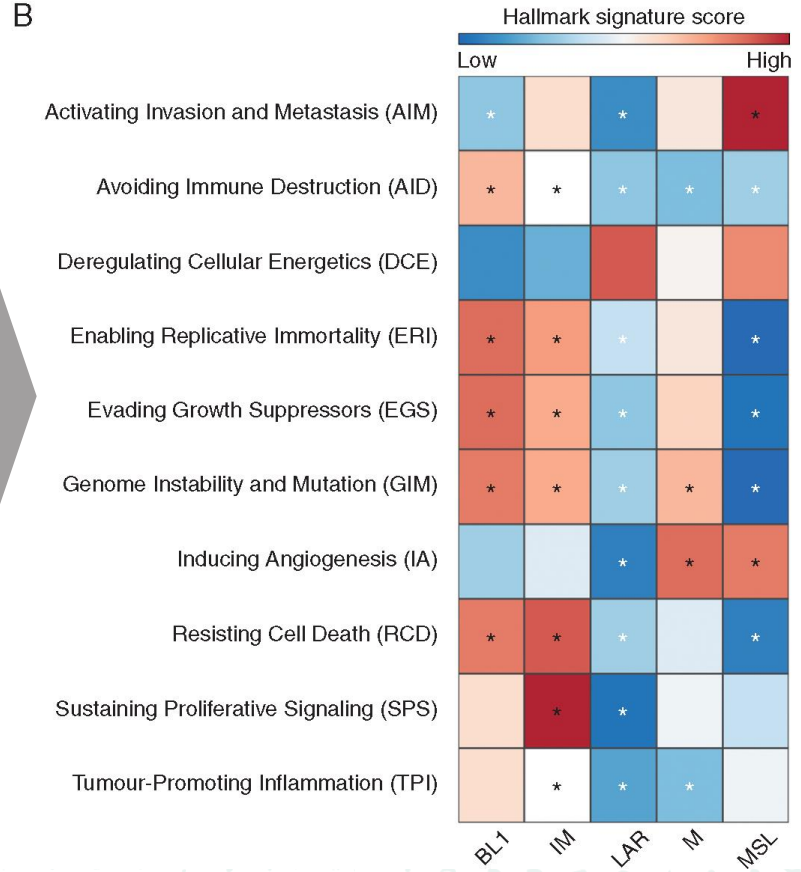
Advancements in molecular diagnostics leads to the fragmentation of cancer indications



Mutation Frequency (%)

	ALL	BL1	IM	LAR	M	MSL
TP53	80	92	81	75	80	58
MUC16	21	17	21	17	33	19
PIK3CA	20	5	16	55	12	23
AHNAK2	19	15	26	13	14	26
SYNE1	17	18	25	15	10	6
AHNAK	13	18	8	11	12	13
DNAH11	12	8	14	15	18	3
USH2A	11	12	10	13	14	3
DNAH2	11	6	11	13	12	13
MLL2	10	14	7	9	6	10
KMT2C	8	6	8	19	2	6
HERC2	8	9	7	11	12	0
DNAH5	8	12	5	8	6	10
RYR2	8	10	11	4	2	10
AKAP9	7	5	5	13	8	3
UTRN	7	4	15	8	2	0
NOTCH1	7	6	7	2	14	3
BIRC6	7	8	5	11	6	0
PTEN	6	5	5	11	6	3
RB1	6	11	3	4	8	0
COL12A1	6	6	11	4	2	0
ATR	5	3	4	6	10	6
NCOR2	5	4	11	4	4	0
STAB2	5	4	3	2	12	3
BRCA1	5	4	5	2	10	0
THSD7A	4	10	0	6	2	0
NF1	4	3	0	13	0	3
AKT1	3	0	3	13	0	0
CDH1	3	1	0	13	2	0

B



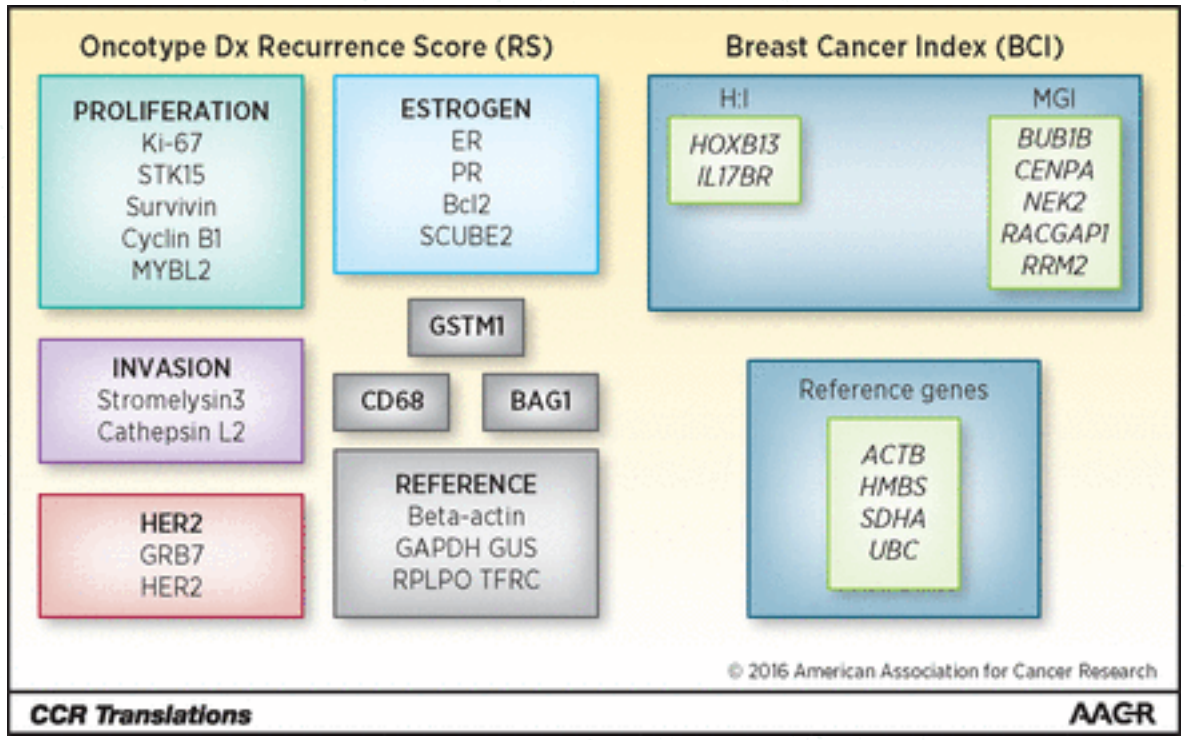
„355 and 195 TNBC samples from the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) and The Cancer Genome Atlas Consortium (TCGA)". „We were able to globally reproduce Lehmann's TNBC classification with BL1, IM, LAR, M and MSL being the more stable subtypes"

Y Bareche et al. (2018) Unravelling triple-negative breast cancer molecular heterogeneity using an integrative multiomic analysis, *Annals of Oncology*, 29, 4:895–902

Resolution of companion diagnostics getting more and more precise

Oncotype Dx RS : **16(+5)**

Foundation One : **315+28**



FOUNDATIONONE® CURRENT GENE LIST*

FoundationOne® is a pan-cancer comprehensive genomic profile, which interrogates the entire coding sequence of 315 cancer-related genes plus introns from 28 genes often rearranged or altered in cancer.

CURRENT GENE LIST									
ABL1	BRAF	CHEK1	FANCC	GATA3	JAK2	MITF	PDCD1LG2	RBM10	STAT4
ABL2	BRCA1	CHEK2	FANCD2	GATA4	JAK3	MLH1	PDGFRA	RET	STK11
ACVR1B	BRCA2	CIC	FANCE	GATA6	JUN	MPL	PDGFRB	RICTOR	SUFU
AKT1	BRD4	CREBBP	FANCF	GID4 (C17orf39)	KAT6A (MYST3)	MRE11A	PDK1	RNF43	SYK
AKT2	BRIP1	CRKL	FANCG	GLI1	KDM5A	MSH2	PIK3C2B	ROS1	TAF1
AKT3	BTG1	CRLF2	FANCL	GNA11	KDM5C	MSH6	PIK3CA	RPTOR	TBX3
ALK	BTK	CSF1R	FAS	GNA13	KDM6A	MTOR	PIK3CB	RUNX1	TERC
AMER1 (FAM123B)	C11orf30 (EMSY)	CTCF	FAT1	GNAQ	KDR	MUTYH	PIK3CG	RUNX1T1	TERT (promoter only)
APC	CARD11	CTNNA1	FBXW7	GNAS	KEAP1	MYC	PIK3R1	SDHA	TET2
AR	CBFB	CTNNB1	FGF10	GPR124	KEL	MYCL (MYCL1)	PIK3R2	SDHB	TGFBR2
ARAF	CBL	CUL3	FGF14	GRIN2A	KIT	MYCN	PLCG2	SDHC	TNFAIP3
ARFRP1	CCND1	CYLD	FGF19	GRM3	KLHL6	MYD88	PMS2	SDHD	TNFRSF14
ARID1A	CCND2	DAXX	FGF23	GSK3B	KMT2A (MLL)	NF1	POLD1	SETD2	TOP1
ARID1B	CCND3	DDR2	FGF3	H3F3A	KMT2C (MLL3)	NF2	POLE	SF3B1	TOP2A
ARID2	CCNE1	DICER1	FGF4	HGF	KMT2D (MLL2)	NFE2L2	PPP2R1A	SLIT2	TP53
ASXL1	CD274	DNMT3A	FGF6	HNF1A	KRAS	NFKBIA	PRDM1	SMAD2	TSC1
ATM	CD79A	DOT1L	FGFR1	HRAS	LMO1	NKX2-1	PREX2	SMAD3	TSC2
ATR	CD79B	EGFR	FGFR2	HSD3B1	LRP1B	NOTCH1	PRKAR1A	SMAD4	TSHR
ATRX	CDC73	EP300	FGFR3	HSP90AA1	LYN	NOTCH2	PRKCI	SMARCA4	U2AF1
AURKA	CDH1	EPHA3	FGFR4	IDH1	LZTR1	NOTCH3	PRKDC	SMARCB1	VEGFA
AURKB	CDK12	EPHA5	FH	IDH2	MAGI2	NPM1	PRSS8	SMO	VHL
AXIN1	CDK4	EPHA7	FLCN	IGF1R	MAP2K1	NRAS	PTCH1	SNCAIP	WISP3
AXL	CDK6	EPHB1	FLT1	IGF2	MAP2K2	NSD1	PTEN	SOCS1	WT1
BAP1	CDK8	ERBB2	FLT3	IKBKE	MAP2K4	NTRK1	PTPN11	SOX10	XPO1
BARD1	CDKN1A	ERBB3	FLT4	IKZF1	MAP3K1	NTRK2	QKI	SOX2	ZBTB2
BCL2	CDKN1B	ERBB4	FOXL2	IL7R	MCL1	NTRK3	RAC1	SOX9	ZNF217
BCL2L1	CDKN2A	ERG	FOXP1	INHBA	MDM2	NUP93	RAD50	SPEN	ZNF703
BCL2L2	CDKN2B	ERRFI1	FRS2	INPP4B	MDM4	PAK3	RAD51	SPOP	
BCL6	CDKN2C	ESR1	FUBP1	IRF2	MED12	PALB2	RAF1	SPTA1	
BCOR	CEBPA	EZH2	GABRA6	IRF4	MEF2B	PARK2	RANBP2	SRC	
BCORL1	CHD2	FAM46C	GATA1	IRS2	MEN1	PAX5	RARA	STAG2	
BLM	CHD4	FANCA	GATA2	JAK1	MET	PBRM1	RB1	STAT3	

SELECT REARRANGEMENTS									
ALK	BRAF	BRD4	ETV4	FGFR1	KIT	MYC	NTRK2	RARA	TMPRSS2
BCL2	BRCA1	EGFR	ETV5	FGFR2	MSH2	NOTCH2	PDGFRA	RET	
BCR	BRCA2	ETV1	ETV6	FGFR3	MYB	NTRK1	RAF1	ROS1	

*Current as of August 18th, 2014.

The analytic validation of FoundationOne®, based on a prior version of the FoundationOne® assay (236 genes, 19 select rearrangements), was published in *Nature Biotechnology*[1] and established the performance specifications required to deliver the high level of accuracy routinely obtained by FoundationOne® for major classes of genomic alteration. This updated version of FoundationOne® met these performance specifications by demonstrating high concordance with genomic profiles of 84 clinical specimens previously profiled on the validated version of FoundationOne®.

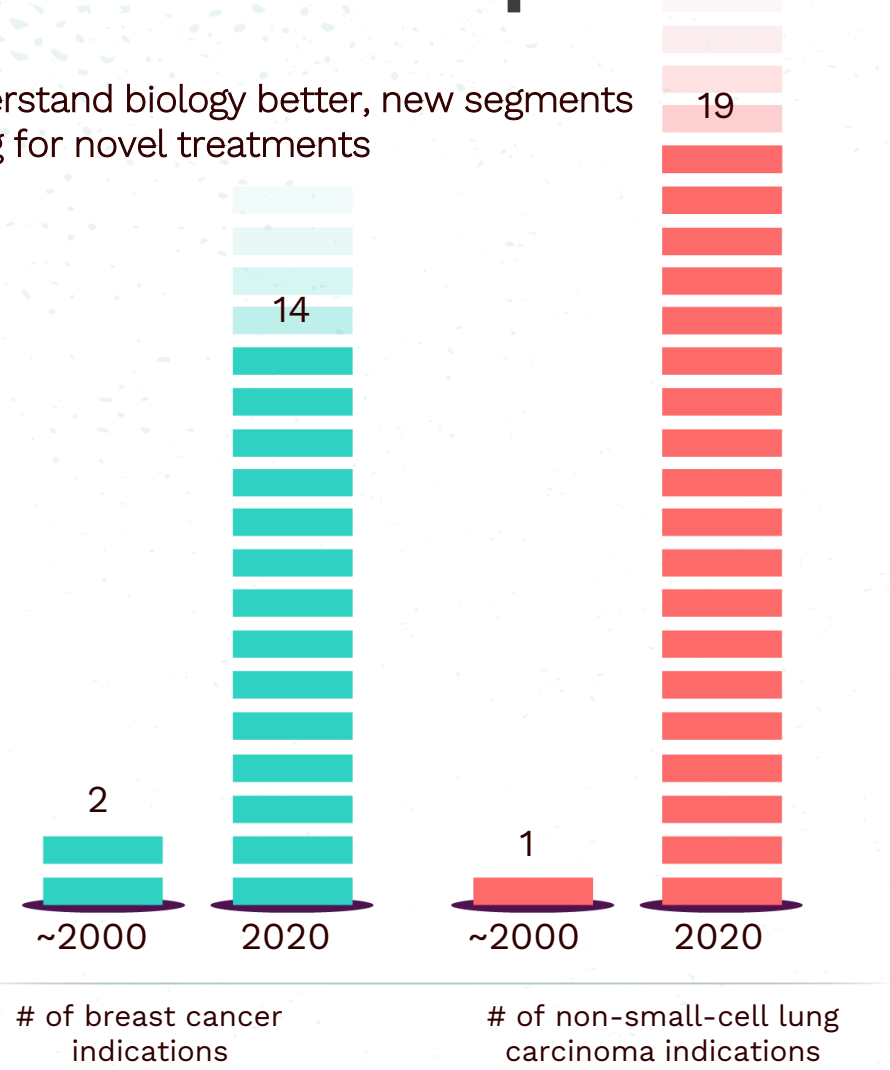
FOUNDATION MEDICINE® | Roche

Examples for indication-agnostic targeted therapy

	NTRKi	PARPi	PD1i
No. patients	+	++	+++
Diagnostic challenge	+++	+	++

Understanding cancer complexity on a scalable way opens markets but poses challenges to pharma R&D

As we understand biology better, new segments are opening for novel treatments



Sources:

1. Evolving genomic classification of NSCLC. Li T et al: J Clin Oncol 2013; 31: 1039–1049.
2. Global Cancer Profiling Market Insights Report 2020-2026 : HTG Molecular Diagnostic, Illumina, NeoGenomics Laboratories, QIAGEN

Key gaps filled by understanding underlying biology

- Relevant target
- First patient to dose
- Patient response
- Overcoming resistance

Better understanding of biology

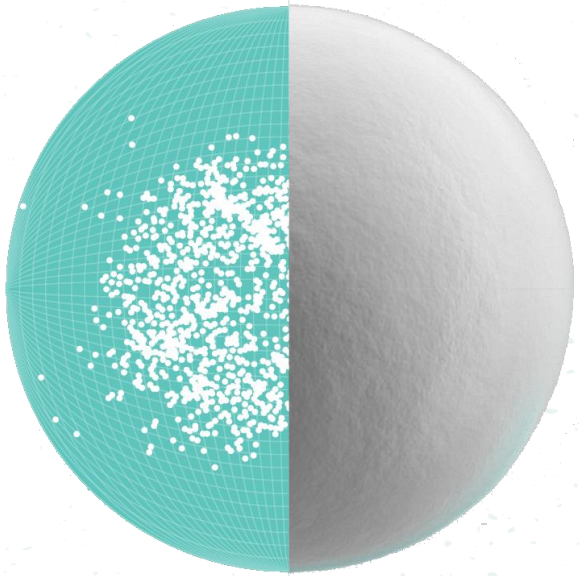
Right intervention, for the right patient, in the right time

More clinical approvals with higher success rate

Concept of Turbine

Integration of biological knowledge into a mechanistic model

Understand behavior of tumors with simulations and predict outcome



Identify responder and non-responder patient populations much earlier during the preclinical phase

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Better understanding of genotype-phenotype relations by signaling modeling

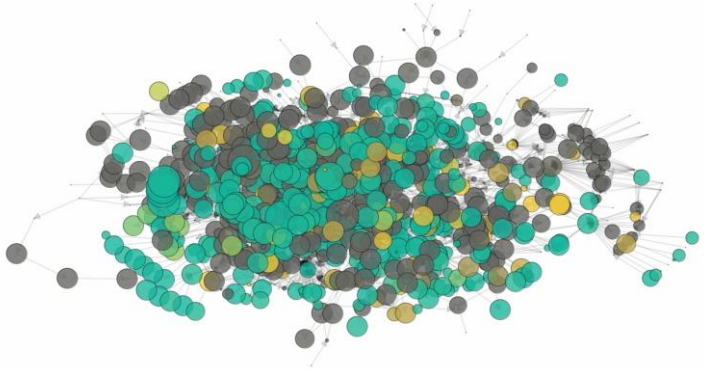
1

Current solutions are correlating genotype with phenotype

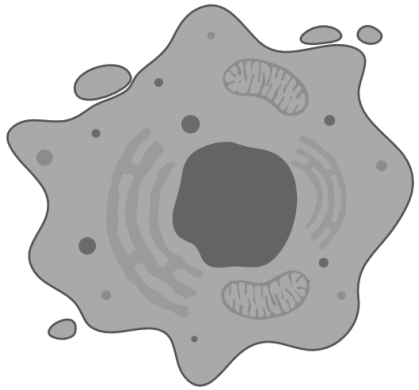
2

Turbine is looking for the hidden features connecting the two layers of complexity

Genotype

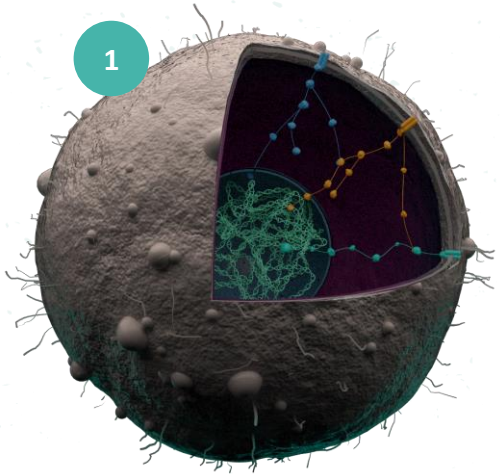


Signaling



Phenotype

Three main pillars of the technology



Simulated Cell model

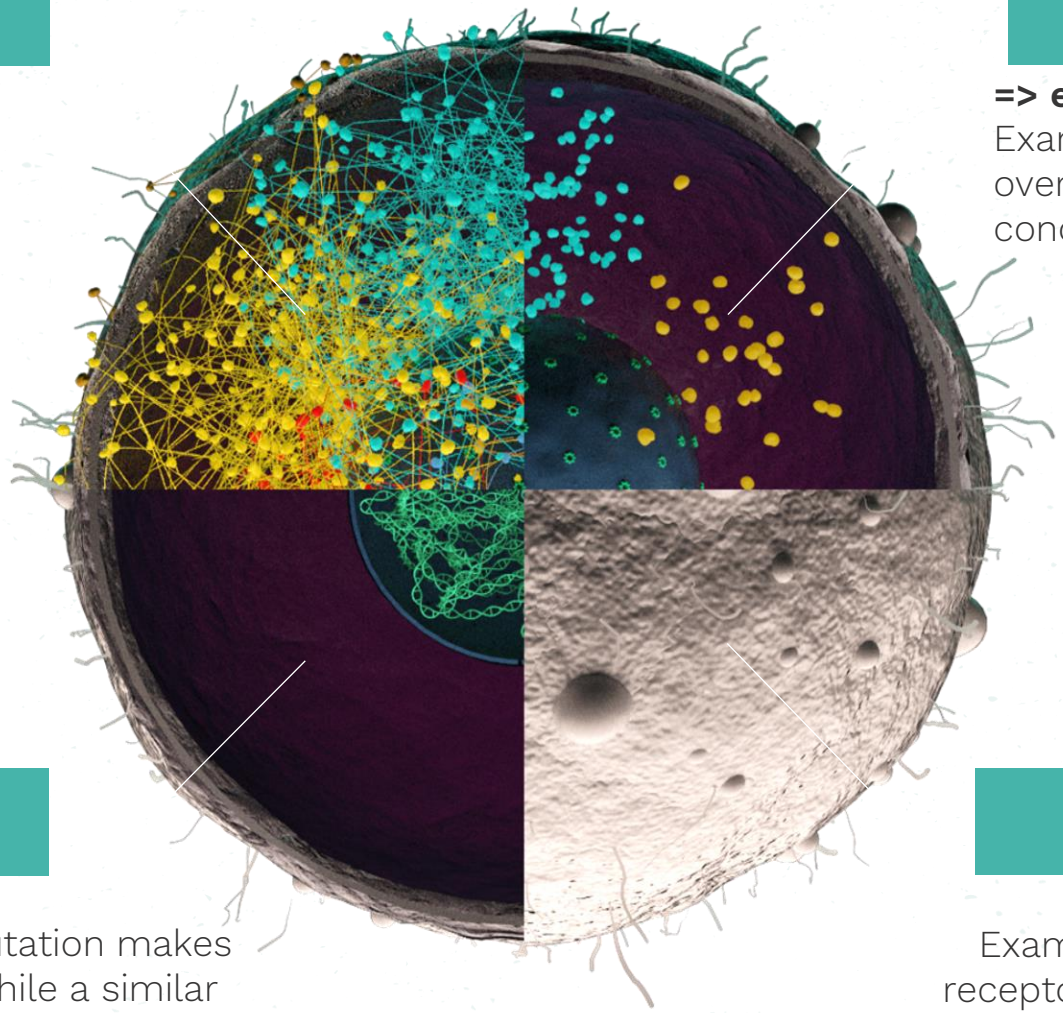
Modelling of phenotypic behavior

Interpretation by biologists guided by AI

Molecular layers of the Simulated Cell model

Wiring diagram

=> signaling network
Manually curated, primarily protein-protein interaction based signaling network with 2500+ nodes and 6200+ interactions.



Transcriptomics

=> est. protein concentration
Example: EGFR receptor overexpression increases its concentration in the model

Genomics

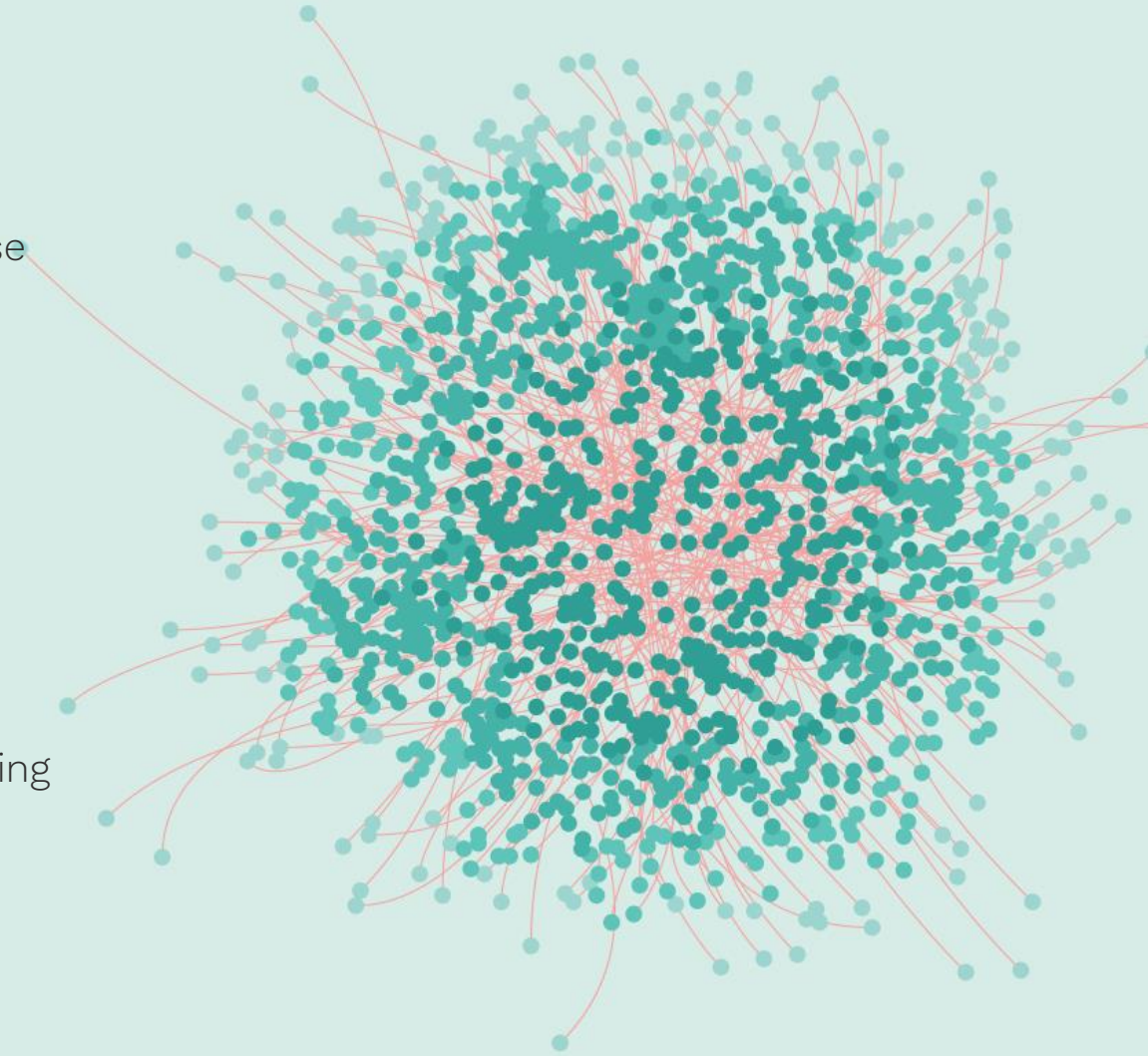
=> protein activity & function
Example: KRAS gene damaging mutation makes the protein constitutively active, while a similar alteration in the P53 gene causes loss-of-function

Compound library

=> inhibitory/activatory effect
Example: by knowing the targets of a receptor tyrosine kinase (RTK) inhibitor, we can inhibit them according to their binding affinities

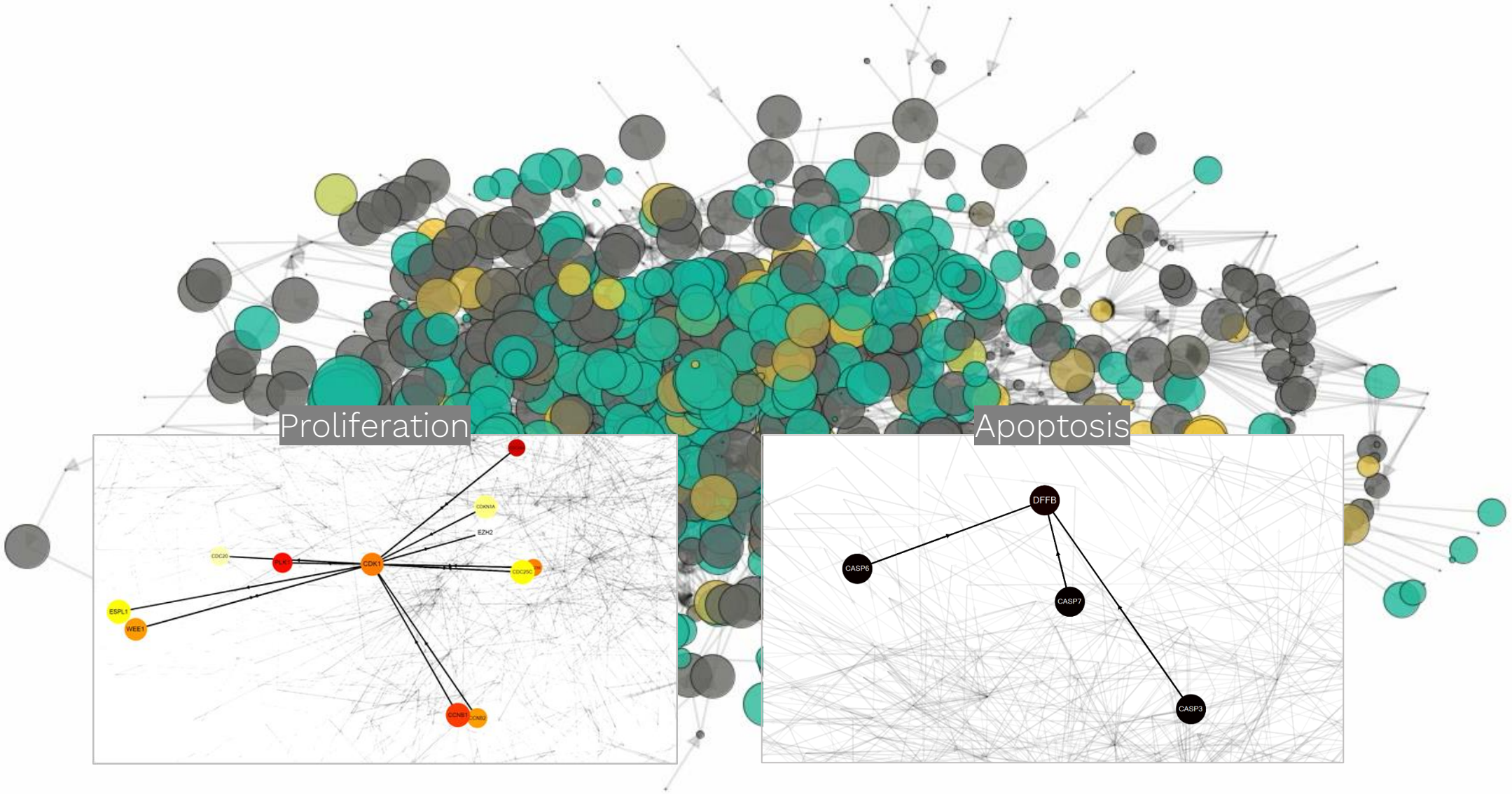
Main signaling pathways covered by the model

1) AMPK
2) Apoptosis
3) B-cell receptor
4) Calcium signaling
5) DNA damage response
6) ER stress
7) ErbB
8) G-proteins
9) Hedgehog
10) Hippo
11) Hypoxia
12) T-cell receptor signaling
13) NFKB
14) JAK/STAT
15) MAPK



16) Microtubule dynamics
17) NFKB
18) Notch
19) p38/JNK
20) PKA
21) PLC
22) Proliferation
23) Proteastasis/Akt/mTOR/
24) RTK signaling
25) Steroid signaling
26) TGFB
27) Toll-like receptor signaling
28) VEGF
29) WNT

Modelling of phenotypic behavior



Three steps of validation

Retrospective

Prospective

Biochemistry

In vitro vs. *in silico*
IC50

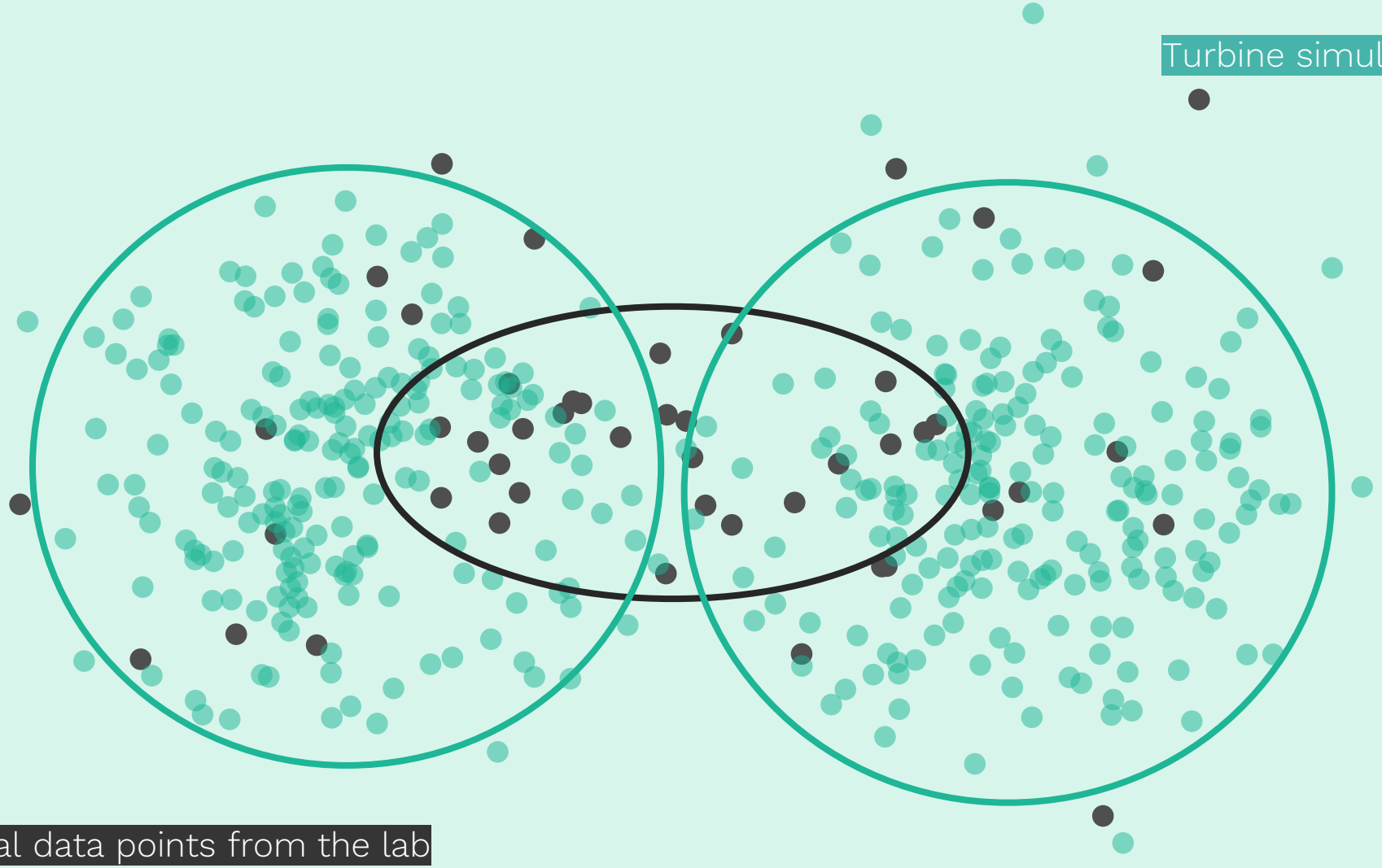
Biology

CRISPR KO benchmarking + Biological hypothesis testing

Translational

Experimental validation of predictions

Interpretation by biologists and AI



We’ve built our patent-protected Simulated Cell platform to understand biology early and at scale

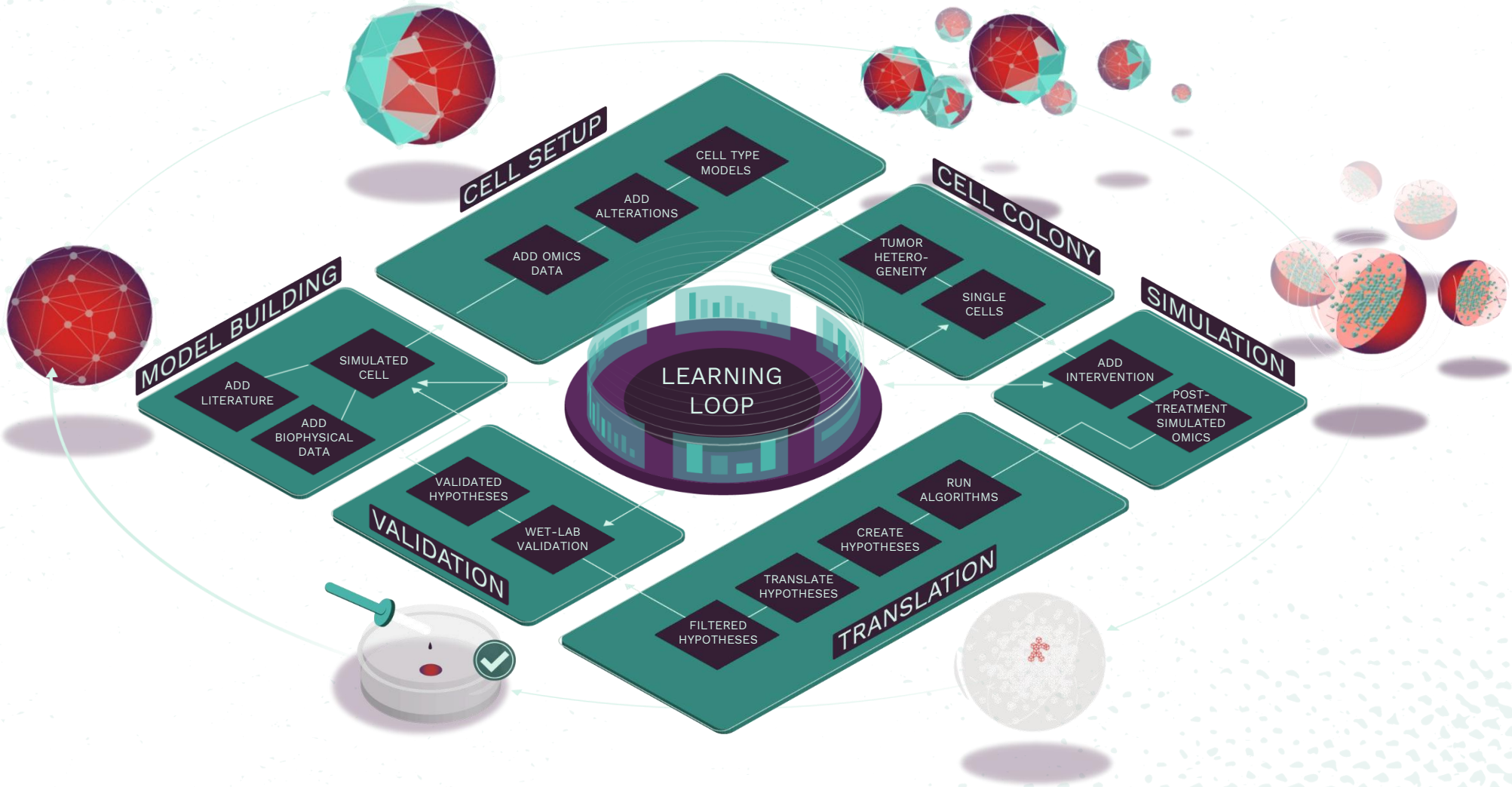
Key features of the Simulated Cell

Model building

- Manually curated general network
- Based on molecular biology literature, trained on proprietary *in vitro* data
- 2.500+ nodes in 23 signaling pathways
- 6.000+ interactions

Already modeled

- 200+ patients’ data
- 611 cell lines
- 185 drugs in monotherapy and combinations



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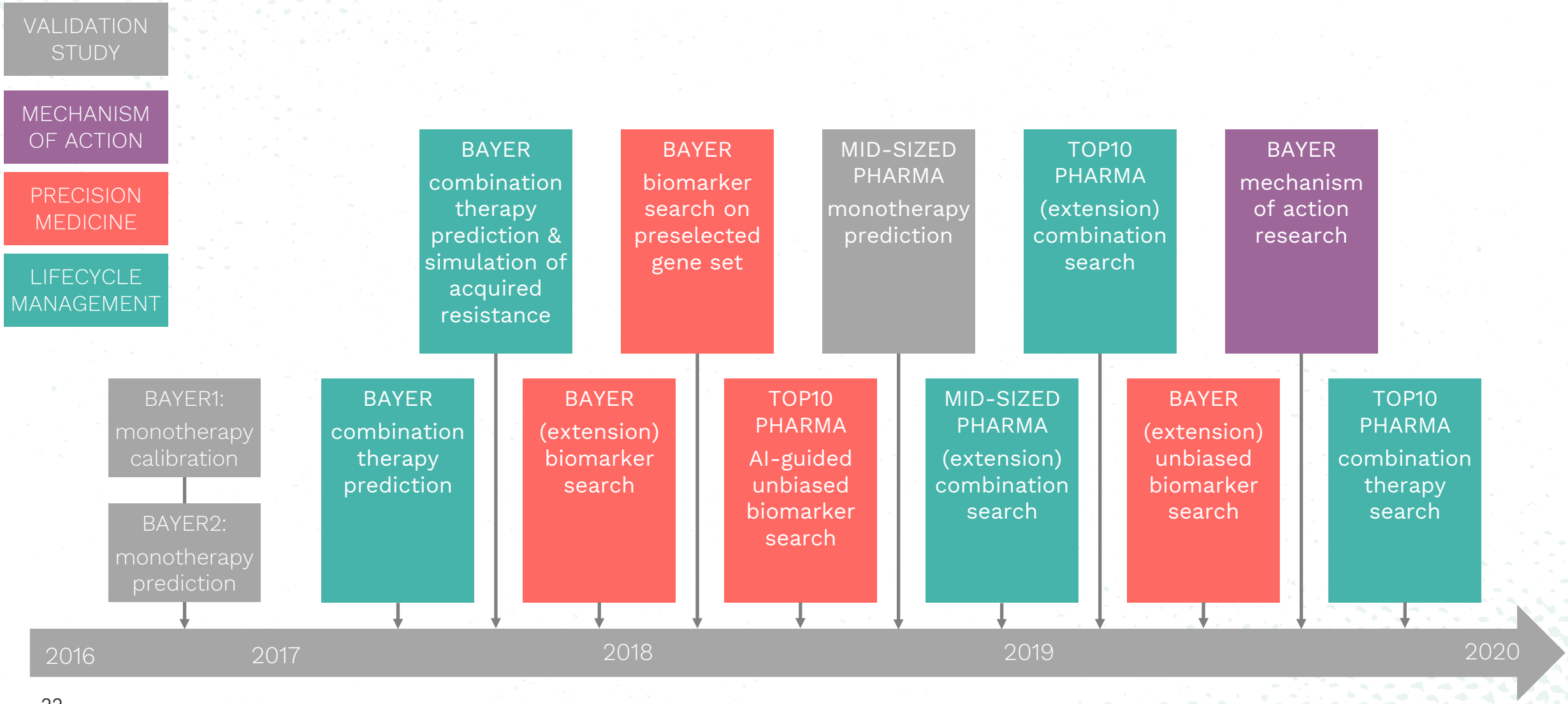
Turbine's predictions have changed the fate of several projects with BAYER and other collaborators



Uncovering indication expansion opportunities for a potential blockbuster drug for Bayer (clinical trial running)

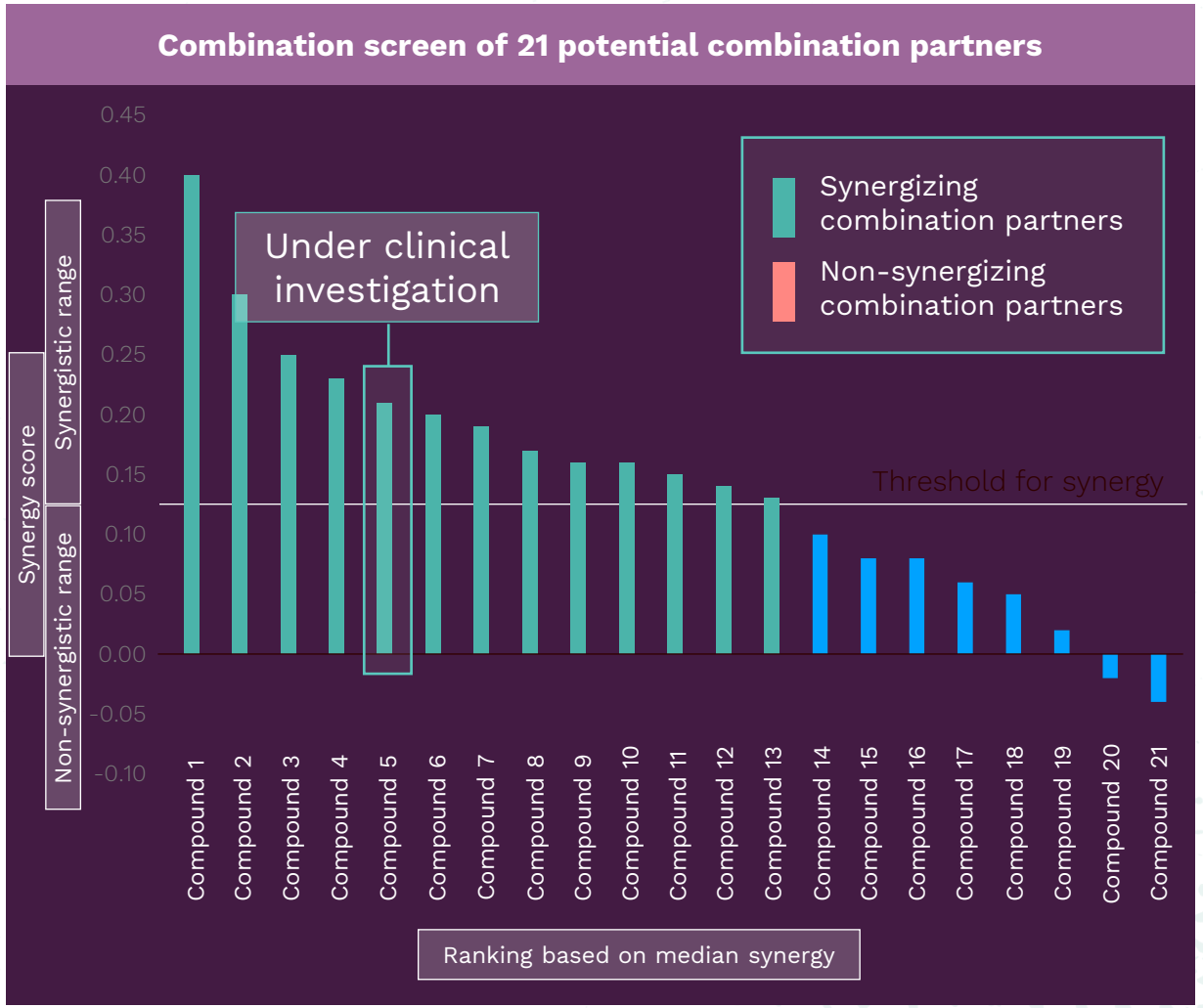
Because Bayer was interested in expanding the potential uses of one of their drugs, they approached us for help in discovering new indications.

Expanding the indications

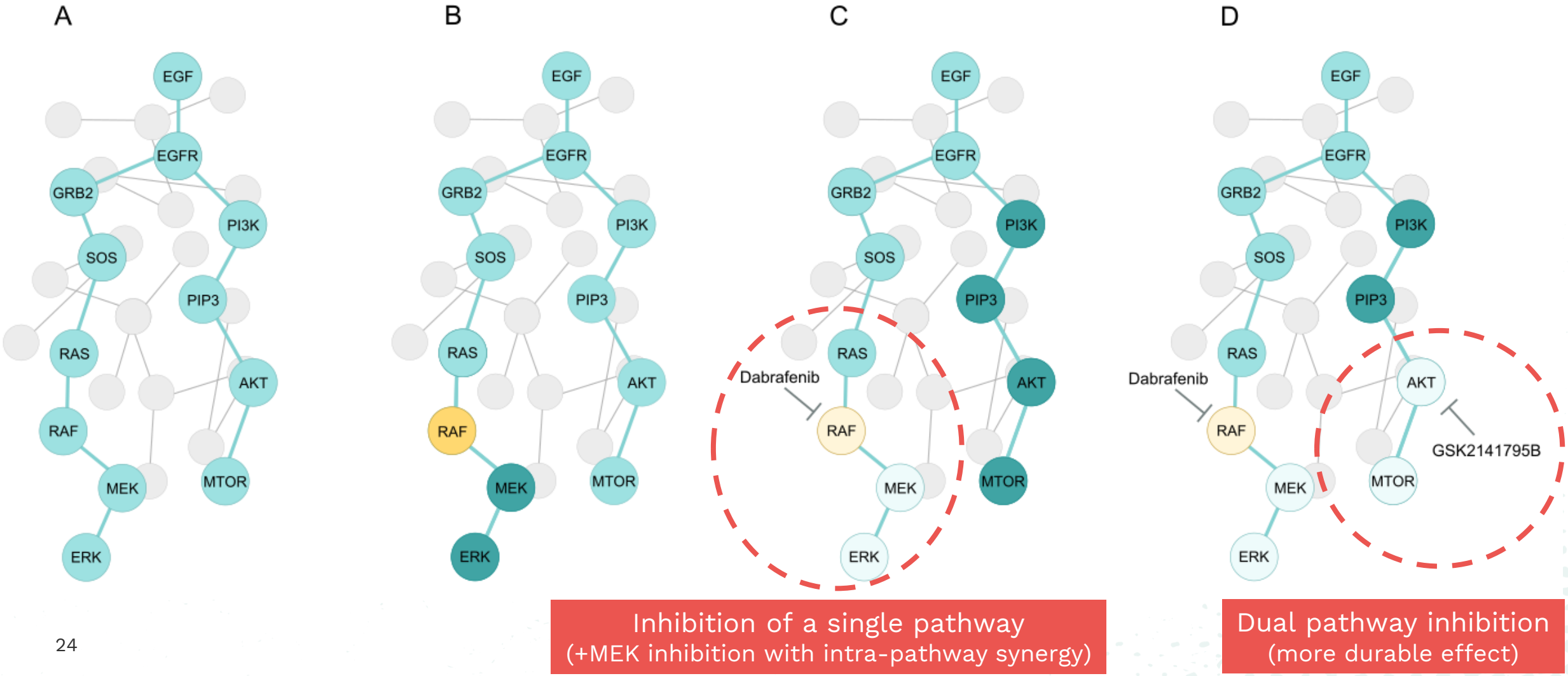
- Bayer wanted to expand its drug either across a greater number of patients (vertically), or over time (horizontally).
- The solution to both was to discover potential drug combination partners.
- Our *in silico* screening delivered **21 combination predictions**, of which **13 were validated *in vitro***.

Outcome

Of the 13 validated predictions, Bayer has chosen one that is currently being investigated in a Phase II clinical trial.



Escapes routes of cancer – ways to develop resistance, blocked by combination therapies



Inhibition of a single pathway
(+MEK inhibition with intra-pathway synergy)

Dual pathway inhibition
(more durable effect)

Identifying a new patient selection biomarker for Bayer's inhibitor beyond a known marker

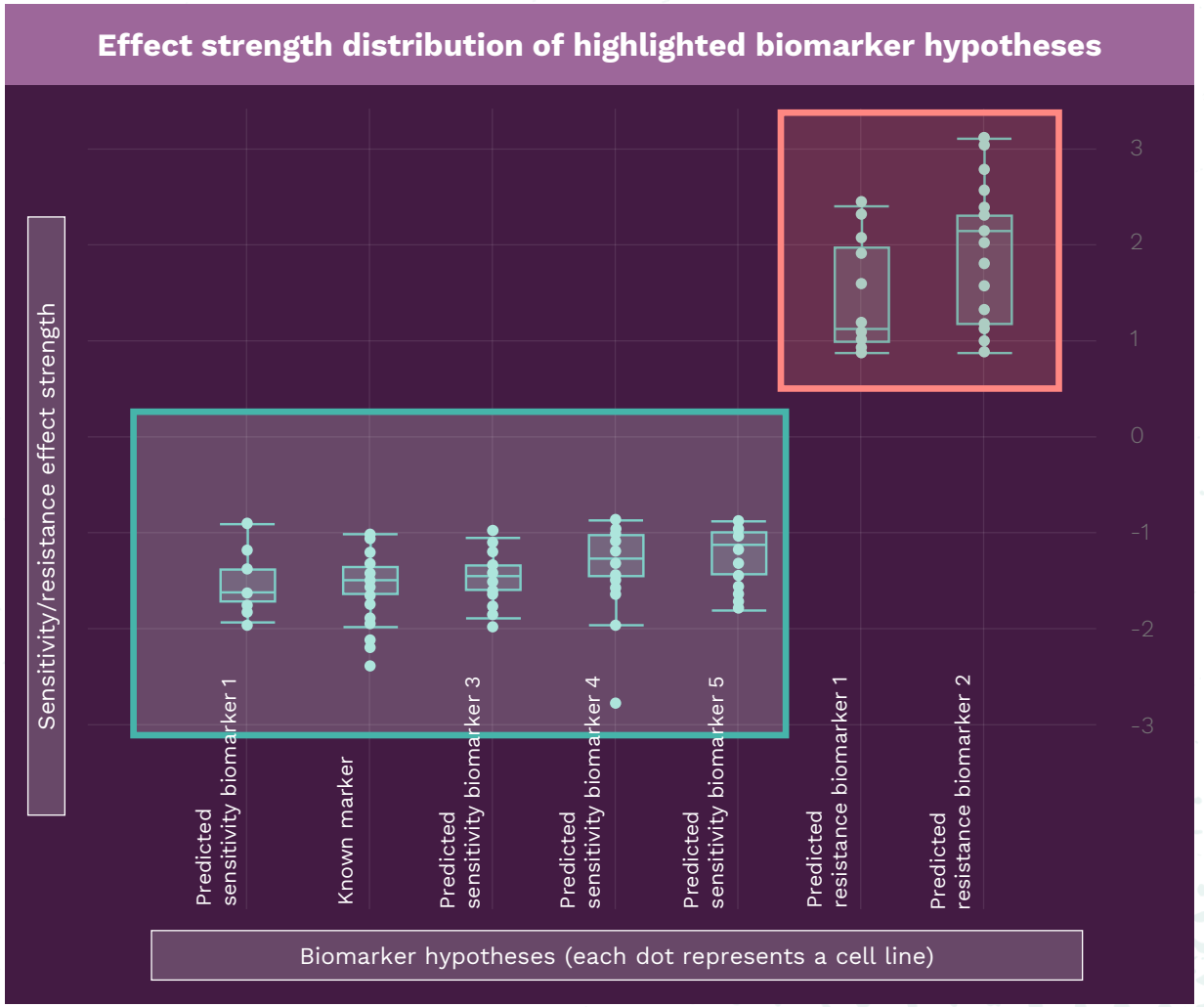
For this collaboration, our partner needed a novel biomarker in order to stratify patients for its compound. However, standard bioinformatics methods couldn't identify anything beyond a known marker

The process

- To identify the novel biomarkers, we needed a high molecular diversity of (simulated) cells that were not otherwise covered by available cell lines.
- Turbine identified several biomarkers, just as strong as – if not stronger than – the known marker.
- After further experiments, we have selected 5 sensitivity and 2 resistance biomarkers.

Outcome

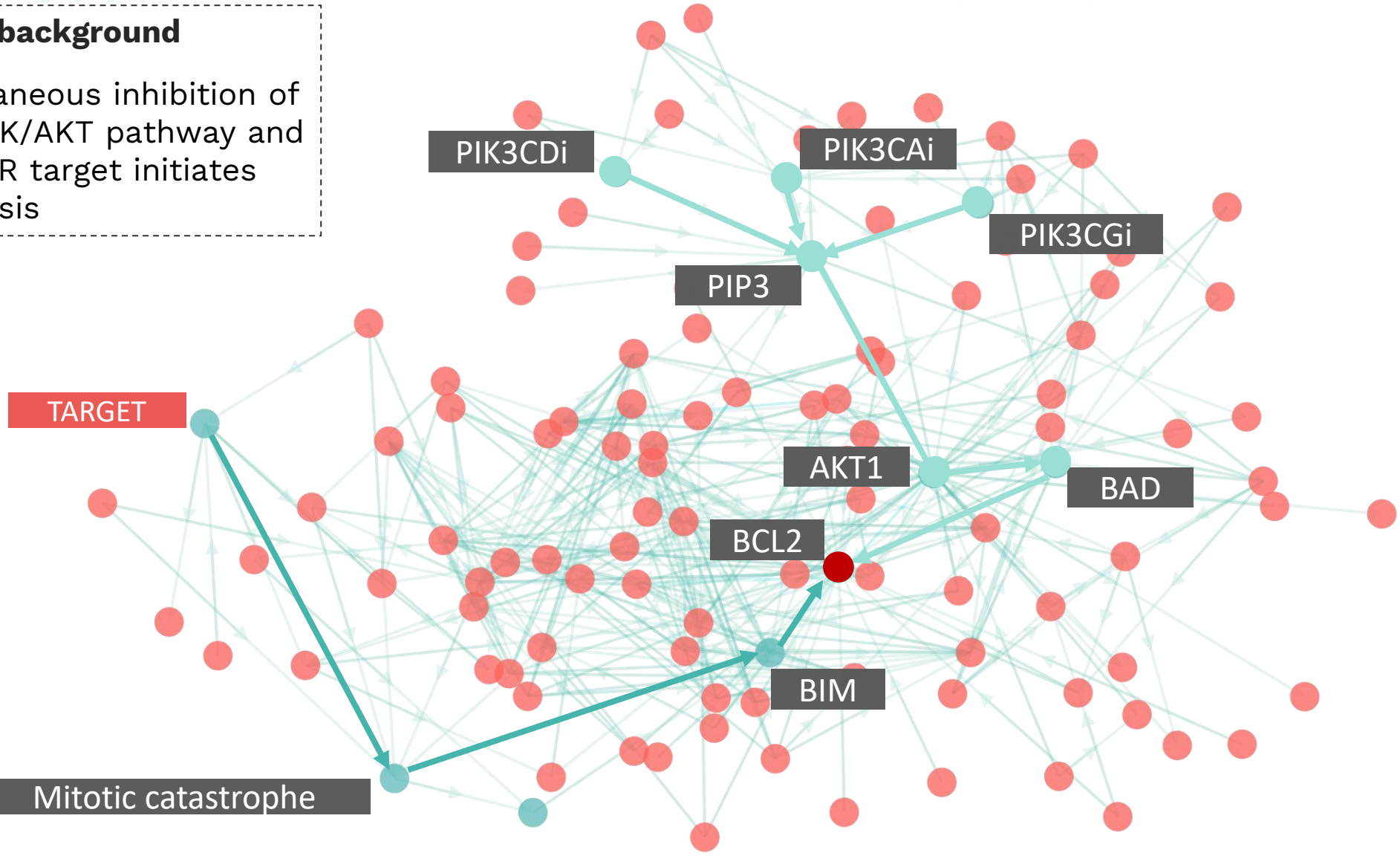
As a result of our work, our predictions were able to guide the Phase II clinical trial planning



Network strategy to find non-trivial biomarkers

Signaling background

- Simultaneous inhibition of the PI3K/AKT pathway and our DDR target initiates apoptosis



Uncovering novel patient sensitivity signatures while modeling resistance in blood cancer patient cells

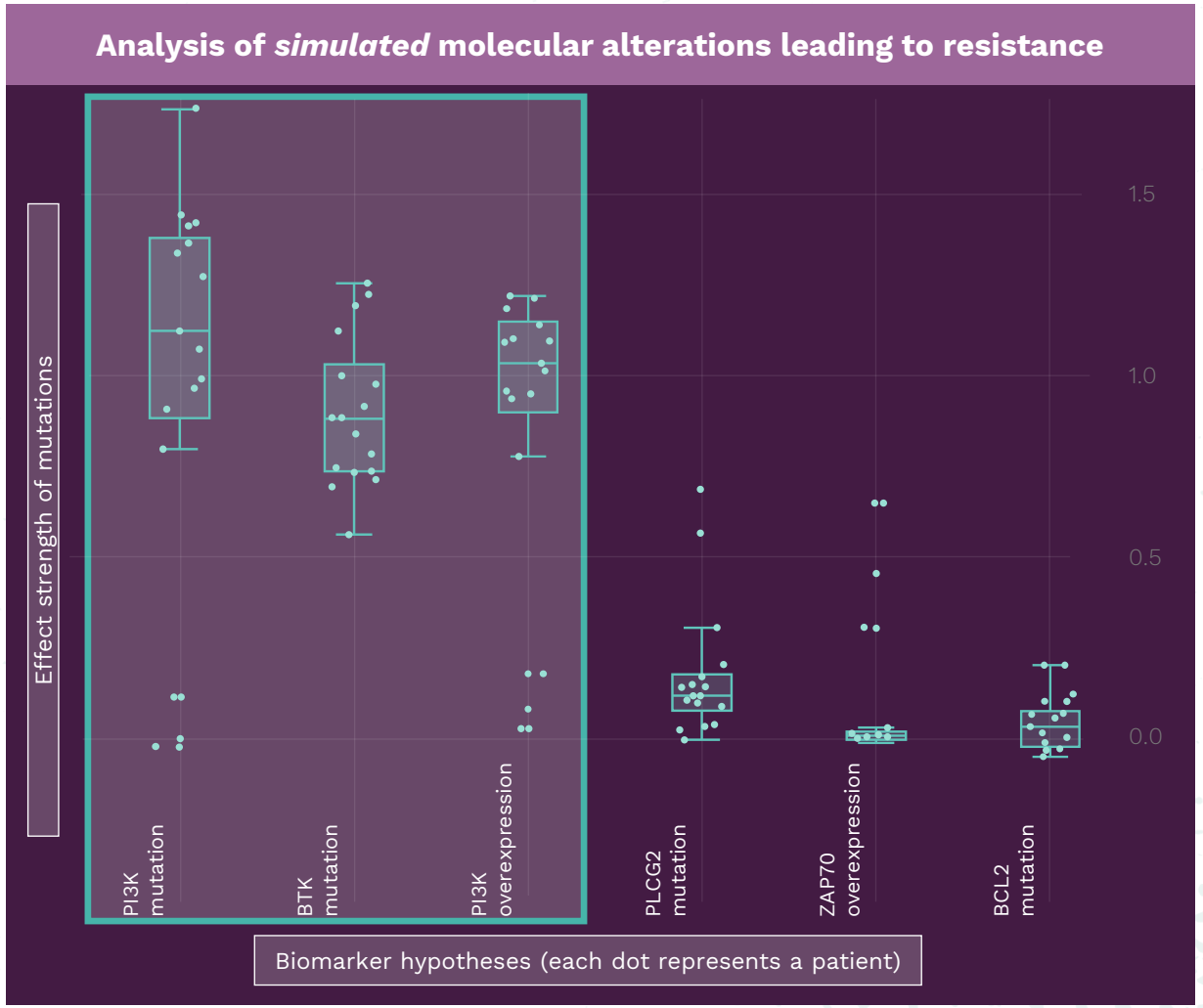
While collaborating with a hematology research group, we were tasked with understanding why certain targeted therapies worked for specific Chronic Lymphocytic Leukemia (CLL) patients, while others would respond to another targeted therapy.

Understanding the disease mechanism

- Our investigation began with approx. 200 patients' mutational and clinical data.
- Simulated Cell™ leveraged the breadth of its dataset to help analyze and predict rates of acquired resistance and success rates for targeted therapies.

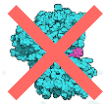
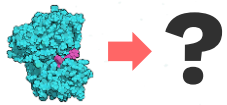
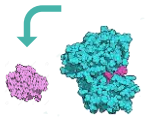
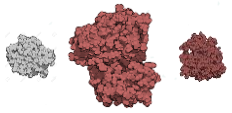
Outcomes

- **Our predictions showed a high occurrence of acquired resistance against ibrutinib among PI3K- and BTK-mutated patients**
- **We were able to identify that gene signatures are more crucial than any single gene biomarker**.

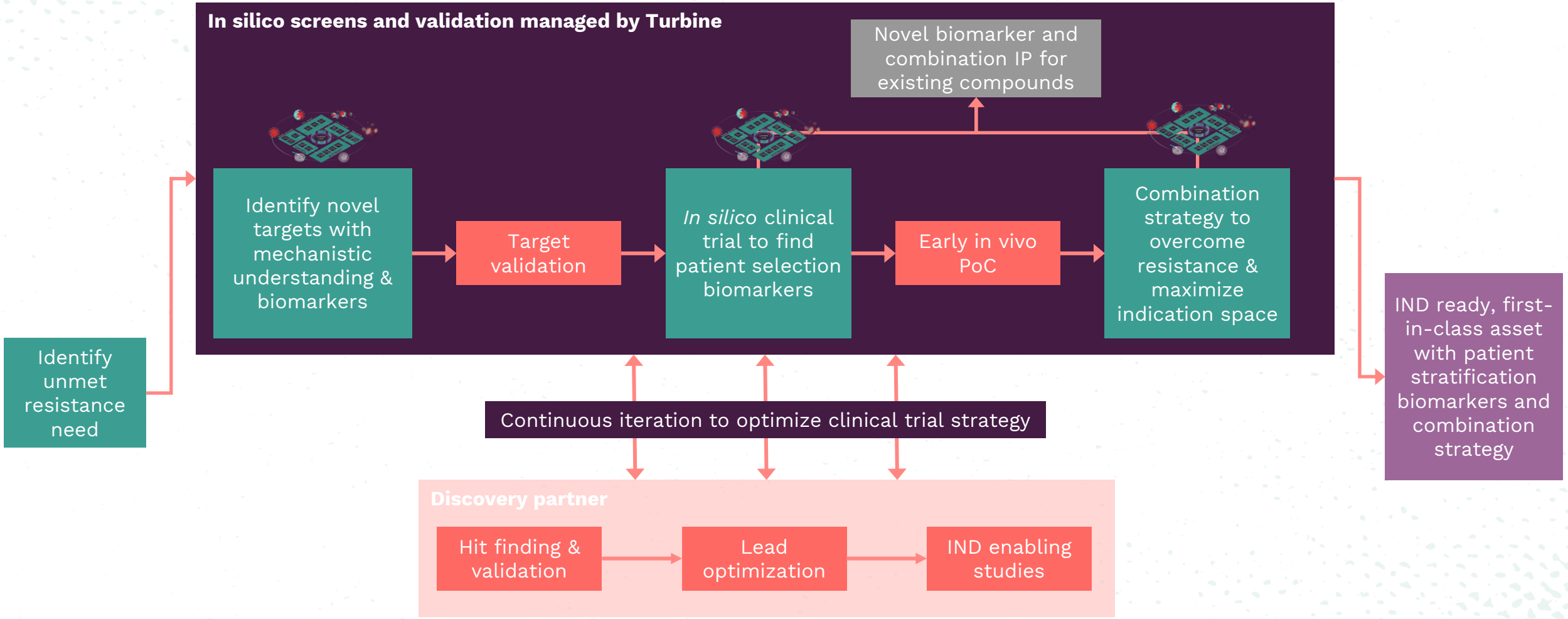


Turbine advantages in finding novel cancer targets compared to CRISPR

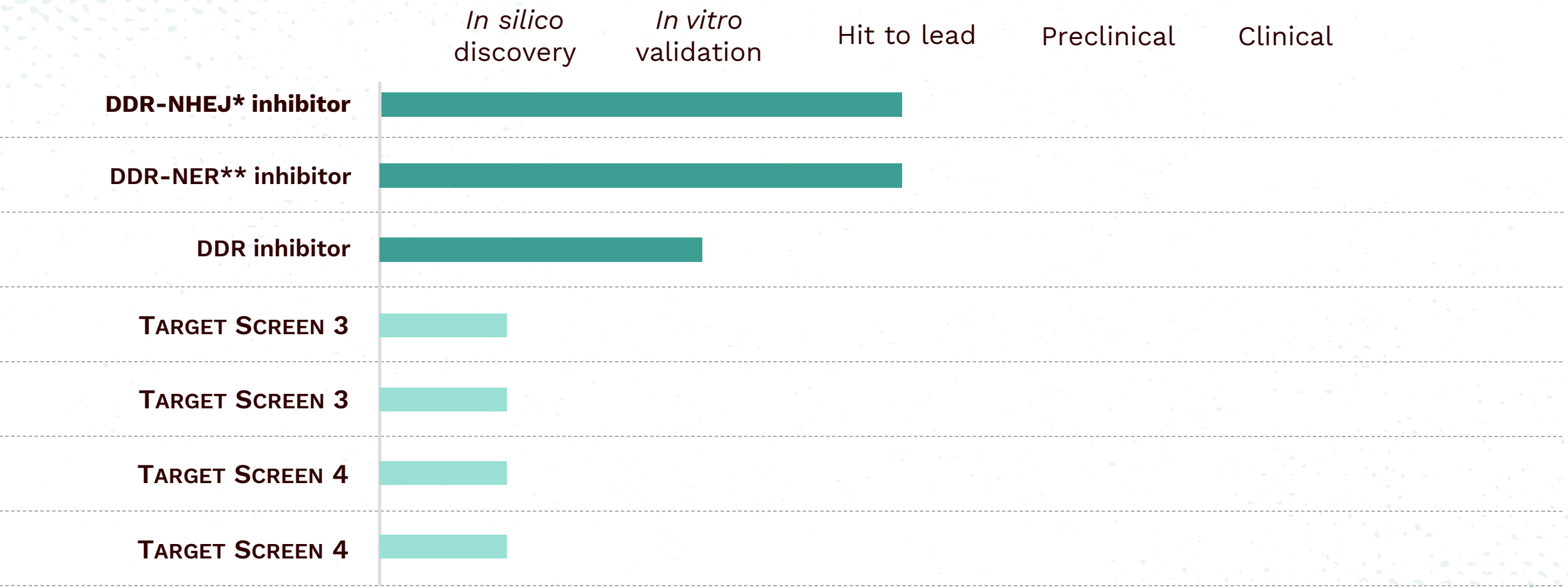
CRISPR overlooks several mechanisms driving cell behaviour and the evolutionary pressures leading to resistance. In comparison, the Simulated Cell™ takes a holistic view of the cell and deploys cell behaviour simulations to quickly reveal the potential of the targets' clinical relevance.

	CRISPR Limitations	Drug Discovery (Dis)Advantage	Turbine Advantage	Turbine Proof
1. Precision Targeting 	Knocks out the entire gene	Pharmacological inhibitors may have different phenotypic effect, gene product may be undruggable	Simulate partial inhibition functional KO to reveal viable targets, identify alternative, druggable targets with similar phenotypic effect	We identified ATR as a promising target, as opposed to DepMap which considers it toxic due to its common essentiality
	Does not yield mechanistic insight	Biomarkers for patient stratification may not be identified	Biomarkers can be identified based on mechanistic understanding	We identified ATM LoF as a sensitivity biomarker for ATRi, currently in Phase 2 validation
2. Durability 	Limited to one gene KO at a time	Tumor may escape through alternative pathway, genetic redundancies may be missed, combination approaches are hard to ID	Combined inhibition of several targets in tandem	We discovered and patented TURB1, a novel target tackling NHEJ-deficinecy driven resistance to PARPi
3. Translatability 	Limited to models which grow in 2D/3D cultures	Available models do not represent patient heterogeneity in many indications	Create cell models from any available sequenced tumor data	We predict clinically validated biomarkers for CLL, a blood cancer for which only a handful of preclinical models are available

Relying on the Simulated Cell™ platform, we turn preclinical research into clinical success



Continuous development of the Simulated Cell enables novel target screens, leading to the expansion of our pipeline



* Non-homologous end joining
** Nucleotide excision repair

1. Who are we?

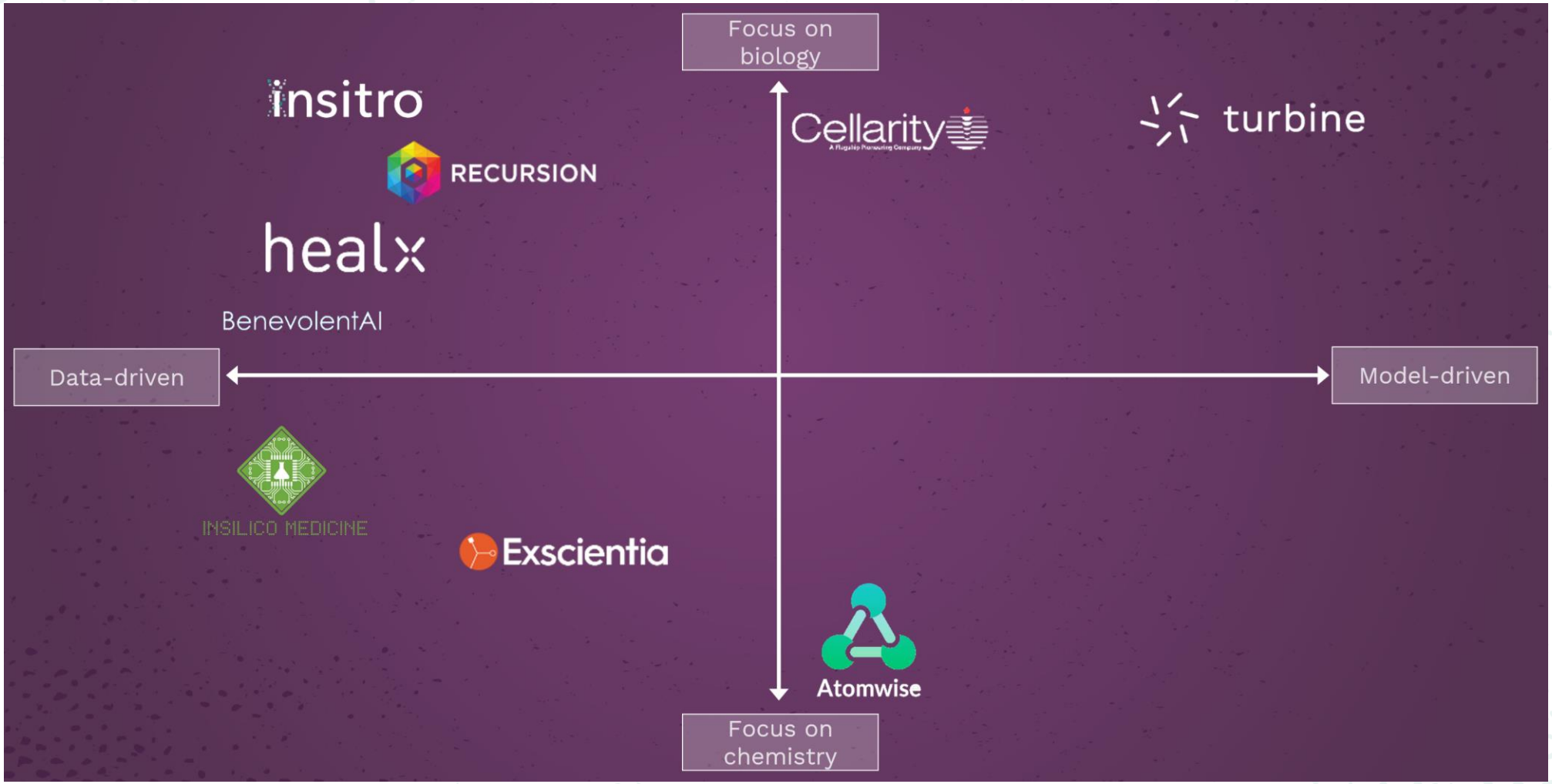
2. Why do we need Turbine?

3. Overview of the technology

4. Simulation benefit in drug discovery

5. Summary and outlook

Unlike other computational platforms, we use one model to guide the entire R&D process by deep biological understanding



So where are we heading?

Conclusions:

- **Deeper biological understanding** is key to decrease biological uncertainty
- **Computational modelling based on network biology** is already helping drug discovery, leading to a **more efficient and rational process**, with feasible economics -> decreases time to the clinic, increases success rates

Current trends:

- Indication agnostic therapies
- Targeted therapies for given molecularly defined patient subgroups
- Increased importance of molecular diagnostics
- *In silico* decision support both in trials and in the clinic

Véleményezés QR-kód-AOK

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AOK: **KZ3**

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