

How networks could be useful?

Simulation-first drug discovery in oncology

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1) Turbine Ltd.

2) Semmelweis University



1. Who are we?

2. Why do we need Turbine?

3. Overview of the technology

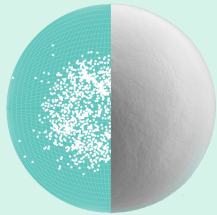
4. Simulation benefit in drug discovery

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
- 1** Hit finding phase
- 1** Initial patent filed

Backed by tech/life sciences VCs

- €10M raised to date



Predictions validated in clinical trials



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

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		Molecular subtypes	Triple negative	HER2+	Luminal B	Luminal A
	Preinvasive cancer	Invasive cancer	Ductal carcinoma in situ (DCIS)	Invasive ductal carcinoma (IDC)		Lobular carcinoma in situ (LCIS)	Invasive lobular carcinoma (ILC)	ER-, PR-, HER2-	ER+, PR+, HER2+
<p>Preinvasive cancer 25%</p> <p>Cells limited to basement membrane</p>	<p>Ductal carcinoma in situ (DCIS) 80%</p> <p>May spread through ducts and distort duct architecture 1% progress to invasive cancer per year Usually unilateral</p>	<p>Lobular carcinoma in situ (LCIS) 20%</p> <p>Does not distort duct architecture Same genetic abnormality as ILC – E-cadherin loss 1% progress per year Can be bilateral</p>	<p>Invasive cancer 75%</p> <p>Extension beyond the basement membrane</p>	<p>Invasive ductal carcinoma (IDC) 79%</p> <p>Usually from DCIS precursor Cause fibrous response, producing a palpable mass on examination Metastasis through lymphatics and blood</p>	<p>Invasive lobular carcinoma (ILC) 10%</p> <p>Usually from LCIS precursor Minimal fibrous response, presents less often with palpable mass Metastasis through abdominal viscera to GI, ovaries, uterus Almost always ER+</p>	<p>% of breast cancers</p> <p>15-20%</p>	<p>10-15%</p>	<p>20%</p>	<p>40%</p>
							HER2	ER+/PR+	
					<p>Histologic grade Level of cell differentiation</p>	High (grade III)			Low (grade I)
					<p>Prognosis Correlates to histologic grade</p>	Poor			Good
					<p>Response to medical therapy</p>	Chemotherapy	Trastuzumab	Endocrine	

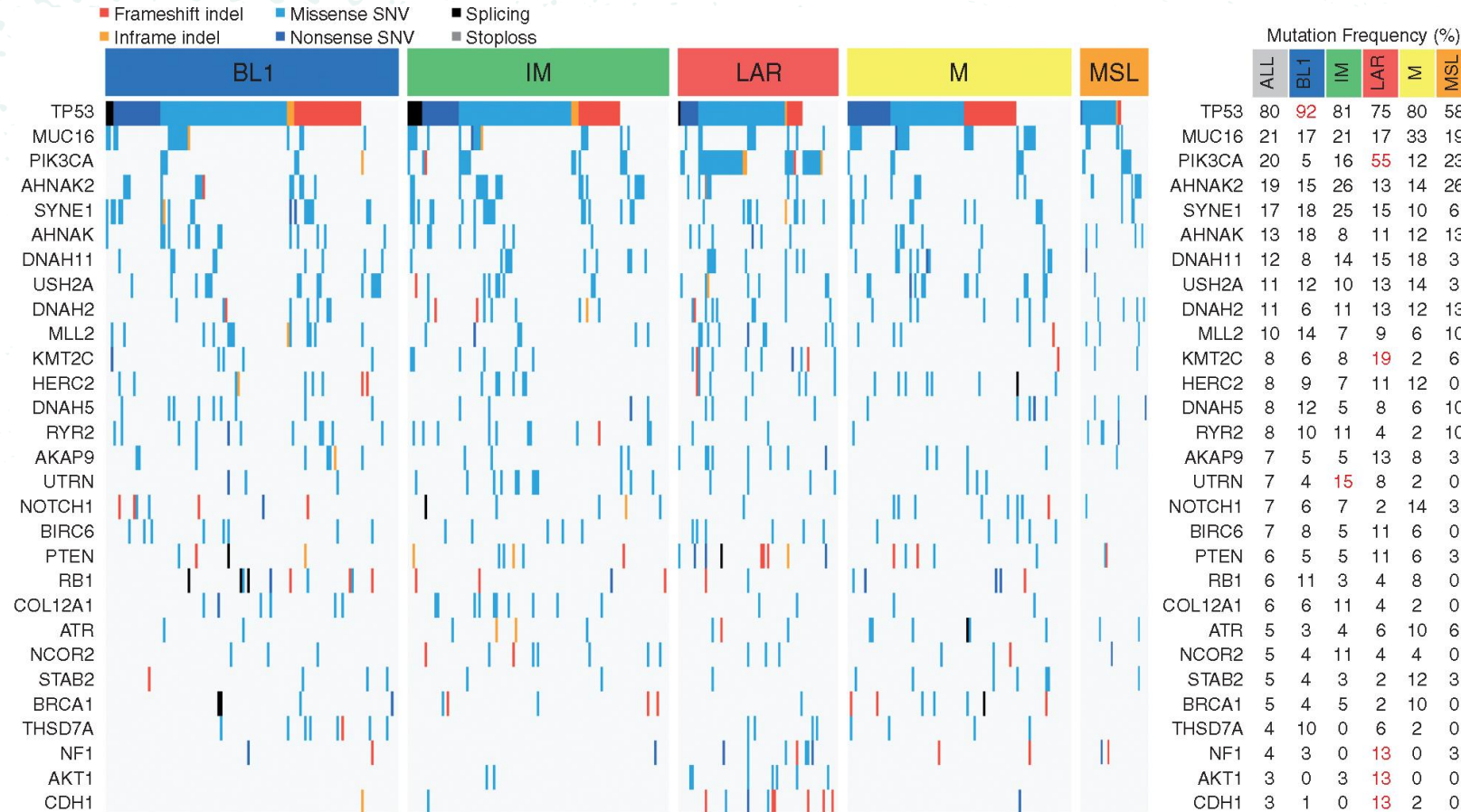
Curr Treat Options Oncol. 2000 Aug;1(3):199-209.
Clin Transl Oncol. 2008 Dec;10(12):777-85.

Nat Clin Pract Oncol. 2007 Sep;4(9):516-25.
Robbins BE

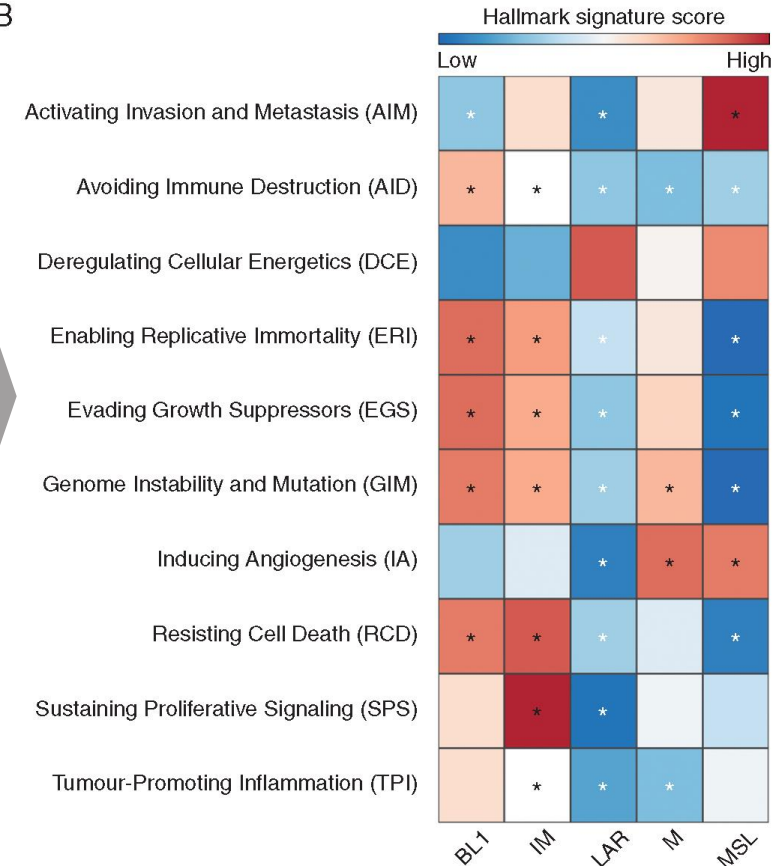
Triple negative tumours respond best to chemotherapy, similar to other aggressive cancers.

Luminal A tumours respond best to endocrine therapy, e.g. antiestrogen or aromatase inhibitor.

Advancements in molecular diagnostics leads to the fragmentation of cancer indications



B



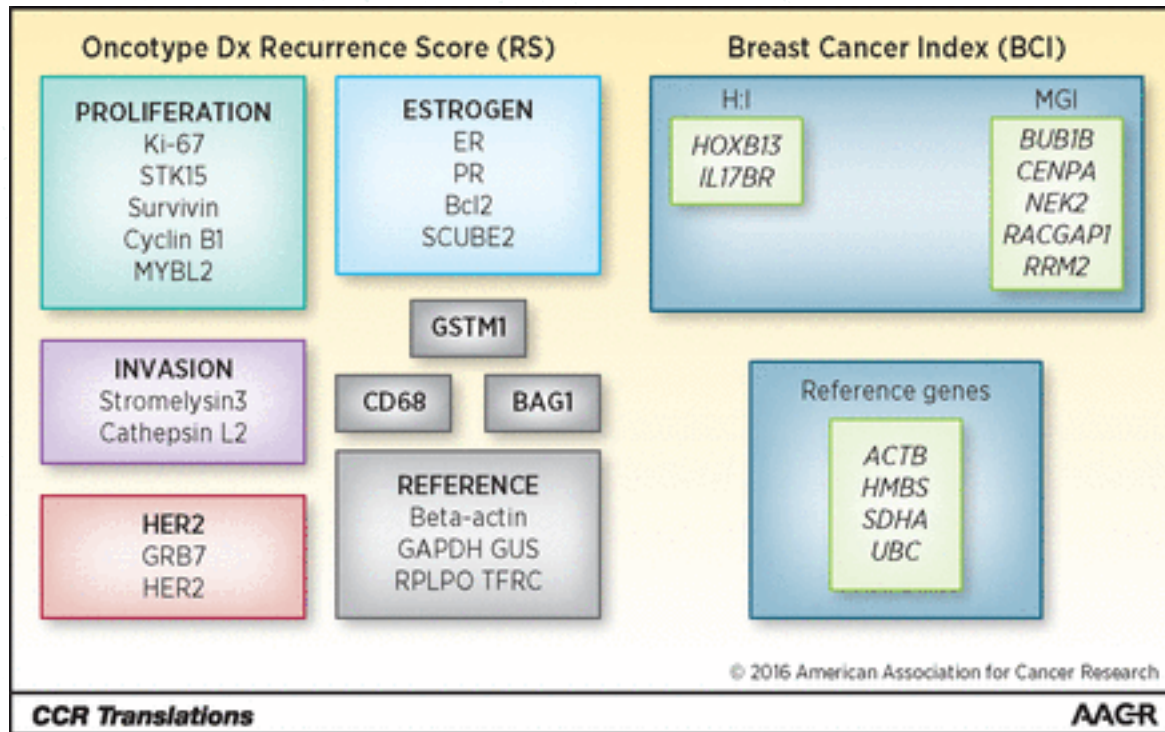
„355 and 195 TNBC samples from the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) and The Cancer Genome Atlas Consortium (TCGA)”. „We were able to globally reproduce Lehmann’s TNBC classification with BL1, IM, LAR, M and MSL being the more stable subtypes”

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	NTF	POC3LG2	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	GEM4 (CTorf39)	KAT5A (MYST3)	HRE11A	PKI	RNF43	SYK
AKT2	BRP1	CRKL	FANCG	GLI1	KDM5A	MSH2	PK3C2B	ROS1	TAF1
AKT3	BTG2	CRF2	FANCL	GNAI1	KDM5C	MSH6	PK3CA	RPTOR	TBK1
ALK	BTX	CSFR	FAS	GNAI3	KDM6A	MTOR	PK3CB	RUNX1	TERC
AMER1 (FAM123B)	CTorf30 (EMSY)	CTCF	FAT1	GNAQ	KDR	MUTYH	PK3CG	RUNX1T1 (promoter only)	TERT
APC	CARD11	CTNNA1	FBXW7	GNA5	KEAP1	MYC	PK3R	SDHA	TET2
AR	CBFB	CTNNB1	FGF10	GPR124	KEL	MYCL (MYCL1)	PK3R2	SDHB	TGFB2
ARAF	CBL	CUL3	FGF14	GRN2A	KIT	MYCN	FLC2	SDHC	TNFAIP3
ARFRP1	CCND1	CYLD	FGF19	GRM3	KLHL6	MYD88	PHS2	SDHD	TNFRSF14
ARD1A	CCND2	DAXX	FGF23	GSK3B	KMT2A (MLL)	NF1	POLD1	SETD2	TOP1
ARD1B	CCND3	DDR2	FGF3	H3F3A	KMT2C (MLL3)	NF2	POLE	SF3B1	TOP2A
ARD2	CEN1	DICER1	FGF4	HGF	KMT2D (MLL2)	NFE2L2	PPP1R1A	SLIT2	TP53
ASXL1	CD274	DHMT3A	FGF6	HNF1A	KRAS	NFKBIA	PRDM1	SMAD2	TSC1
ATM	CD79A	DOT1L	FGFR1	HRAS	LMO1	NKX2-1	PRKX	SMAD3	TSC2
ATR	CD79B	EGFR	FGFR2	HSD3B1	LRP8	NOTCH1	PRKARIA	SHAD4	TSHR
ATRX	CDC73	EP300	FGFR3	HSP90AA1	LYN	NOTCH2	PRKCI	SHARCA4	UZAF1
AURKA	CDH1	EPHA3	FGFR4	IDH1	LZTR1	NOTCH3	PRKDC	SHARCB1	VEGFA
AURKB	CDK12	EPHA5	FH	IDH2	MAGI2	NPM1	PRSS8	SHD	VHL
AXIN1	CDK4	EPHA7	FLCN	IGFBP	HAP2K1	NRAS	PTCH1	SHCAIP	WSP3
AXL	CDK6	EPHBI	FLT1	IGF2	MAP2K2	NSD1	PTEN	SOCS1	WT1
BAP1	CDK8	ERBB2	FLT3	KIB1E	MAP3K4	NTRK1	PTPN11	SOX10	XPO1
BARD1	CDKN1A	ERBB3	FLT4	IKZF1	HAP3K1	NTRK2	GRI	SOX2	ZBTB2
BCL2	CDKN1B	ERBB4	FOXL2	IL7R	MCL1	NTRK3	RAC1	SOX9	ZNF217
BCL2L1	CDKN2A	ERG	FOXP1	RBM8A	MDM2	NUP93	RAD50	SPEN	ZNF703
BCL2L2	CDKN2B	ERRF1	FRS2	INPP4B	MDM4	PAK3	RAD51	SPOP	
BCL6	CDKN2C	ESR1	FUBP1	ISF2	MED12	PALB2	RAF1	SPTA1	
BCOR	CEBPA	EDH2	GABRA6	IRF4	MEF2B	PARK2	RANBP2	SRC	
BCORL1	CHD2	FAM46C	GATA1	IRS2	MEN1	PAX5	RARA	STAG2	
BLM	CHD4	FANCA	GATA2	JAK1	HET	PBRM1	RBI	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, 2016.

The analytic validation of FoundationOne® (based on a prior version of the FoundationOne® assay (236 genes, 18 select rearrangements)), was published in Nature Biotechnology¹ 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 58 clinical specimens previously profiled on the validated version of FoundationOne®.

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Examples for indication-agnostic targeted therapy



No. patients

+

++

+++

Diagnostic challenge

+++

+

++



NTRKi



PD1i

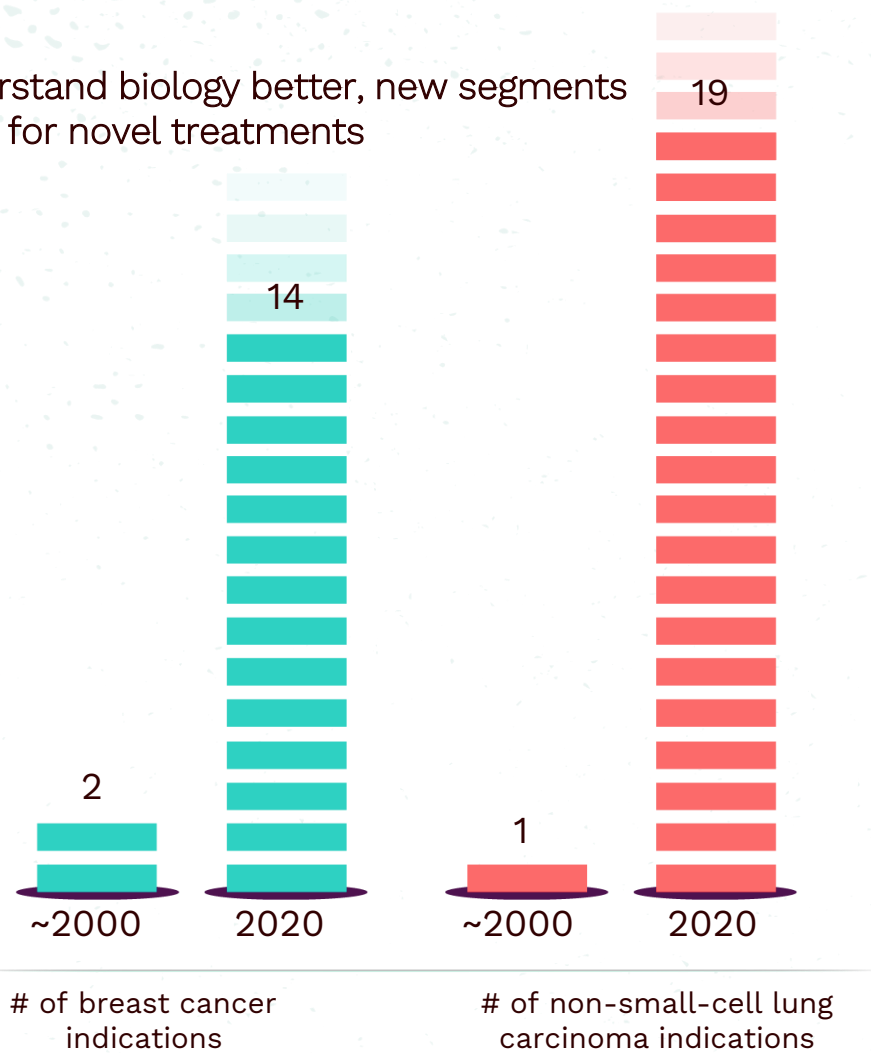
Understanding cancer complexity on a scalable way opens markets but poses challenges to pharma R&D



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



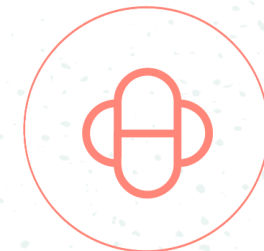
Relevant target



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

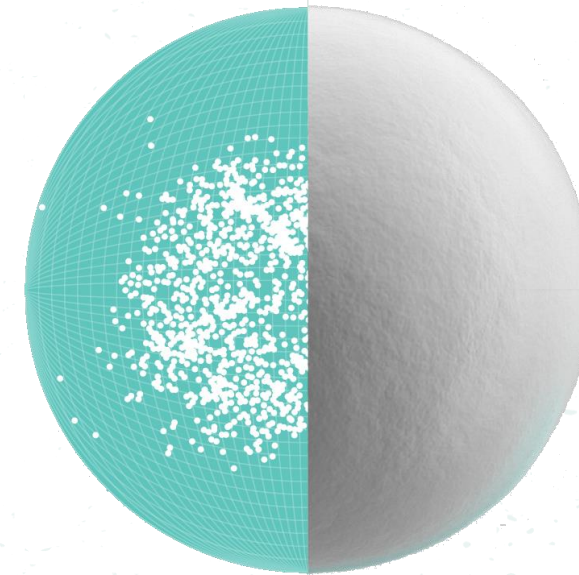
Concept of Turbine



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

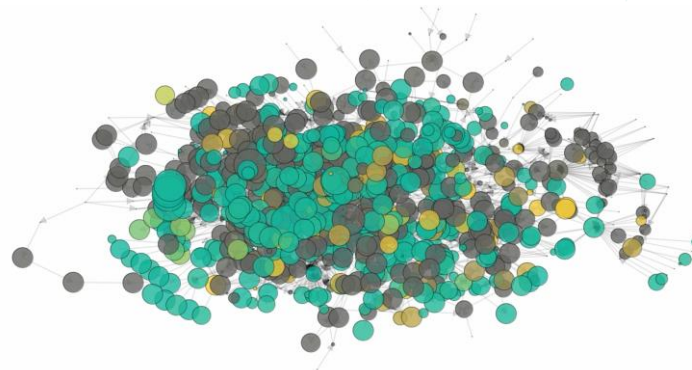
Current solutions are correlating genotype with phenotype

2

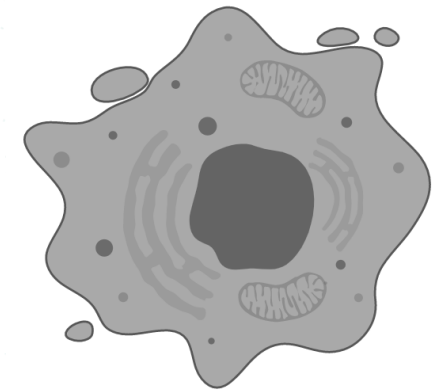
Turbine is looking for the hidden features connecting the two layers of complexity



Genotype

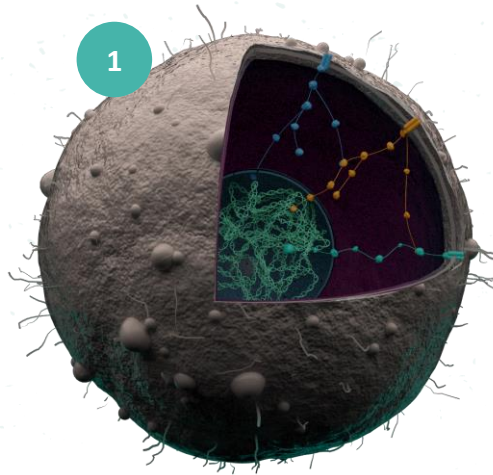


Signaling



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.

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

Transcriptomics

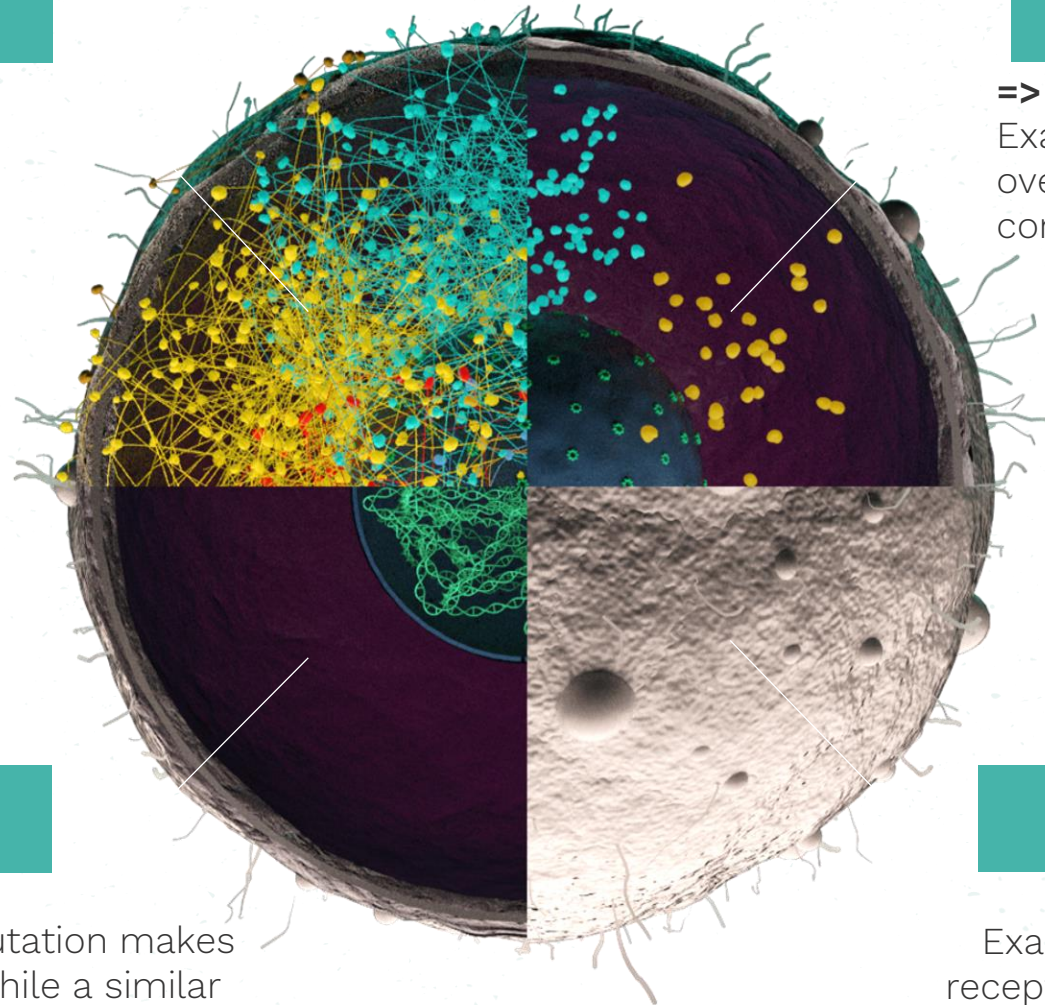
=> est. protein concentration

Example: EGFR receptor overexpression increases its concentration in the model

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

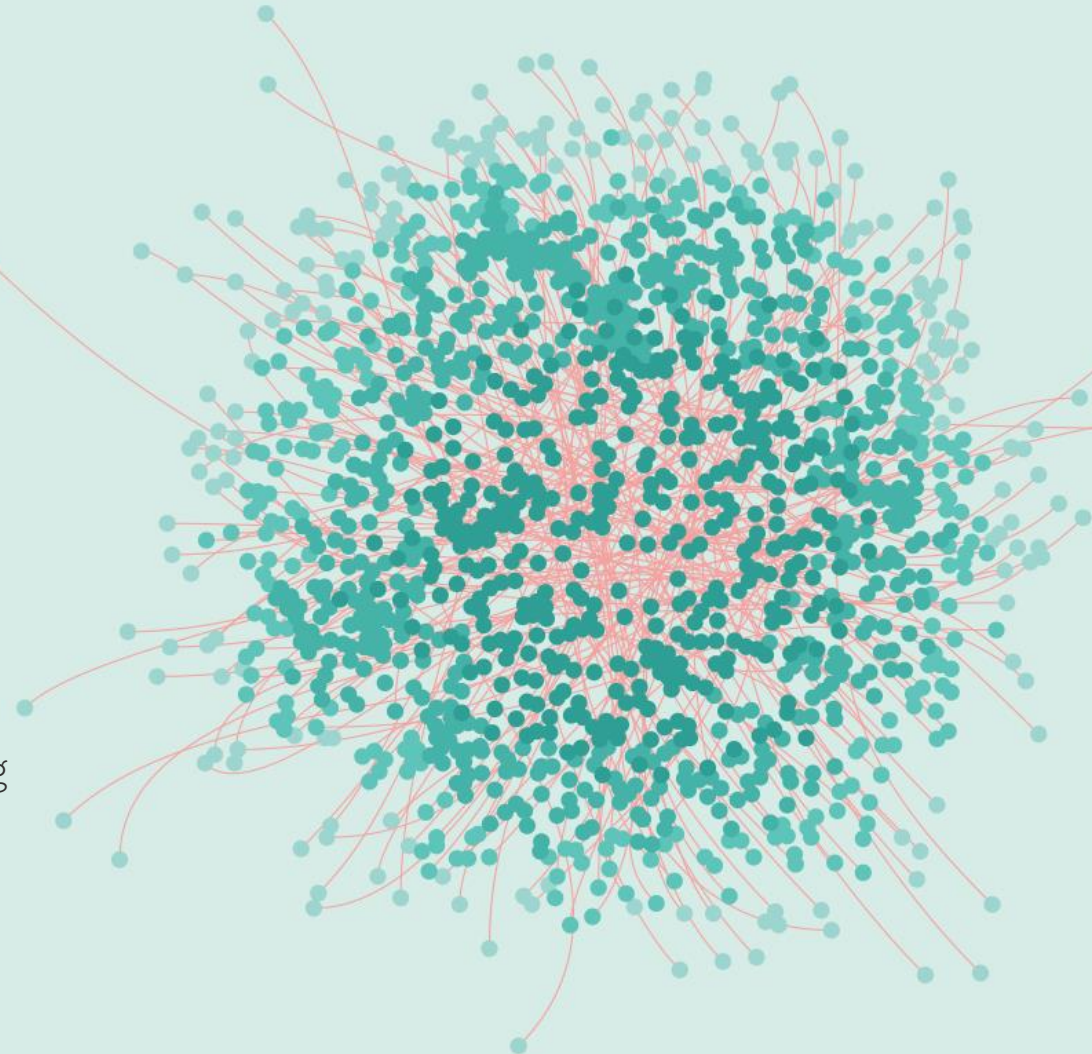


Main signaling pathways covered by the model

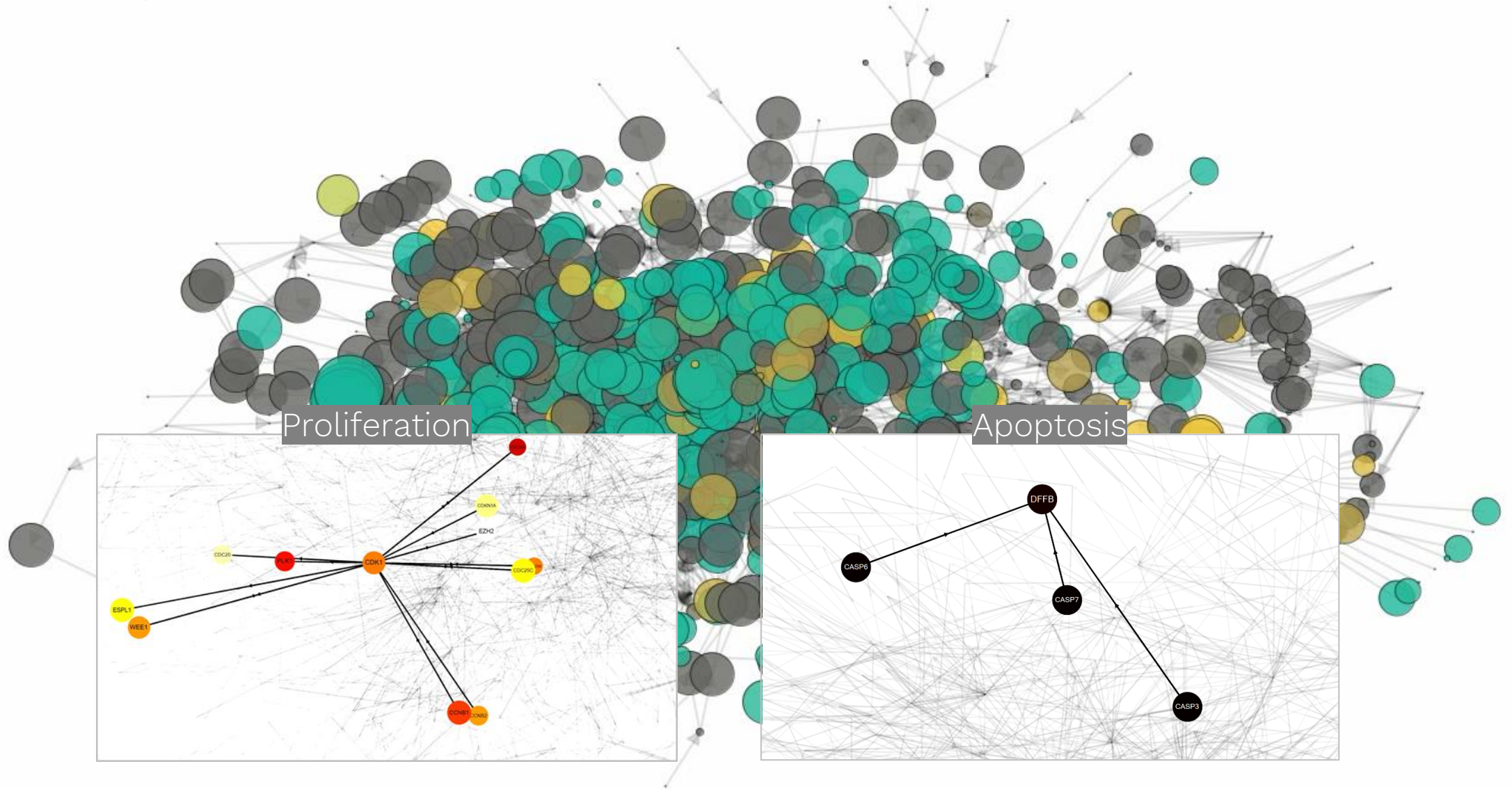


- 1) AMPK
- 2) Apoptosis
- 3) B-cell receptor
- 4) Calcium signaling
- 5) DNA damage response
- 6) ER stress
- 7) ErbB
- 8) G-proteins
- 9) Hedgehog
- 10) Hippo
- 11) Hypoxia
- 12) T-cell receptor signaling
- 13) NFKB
- 14) JAK/STAT
- 15) MAPK

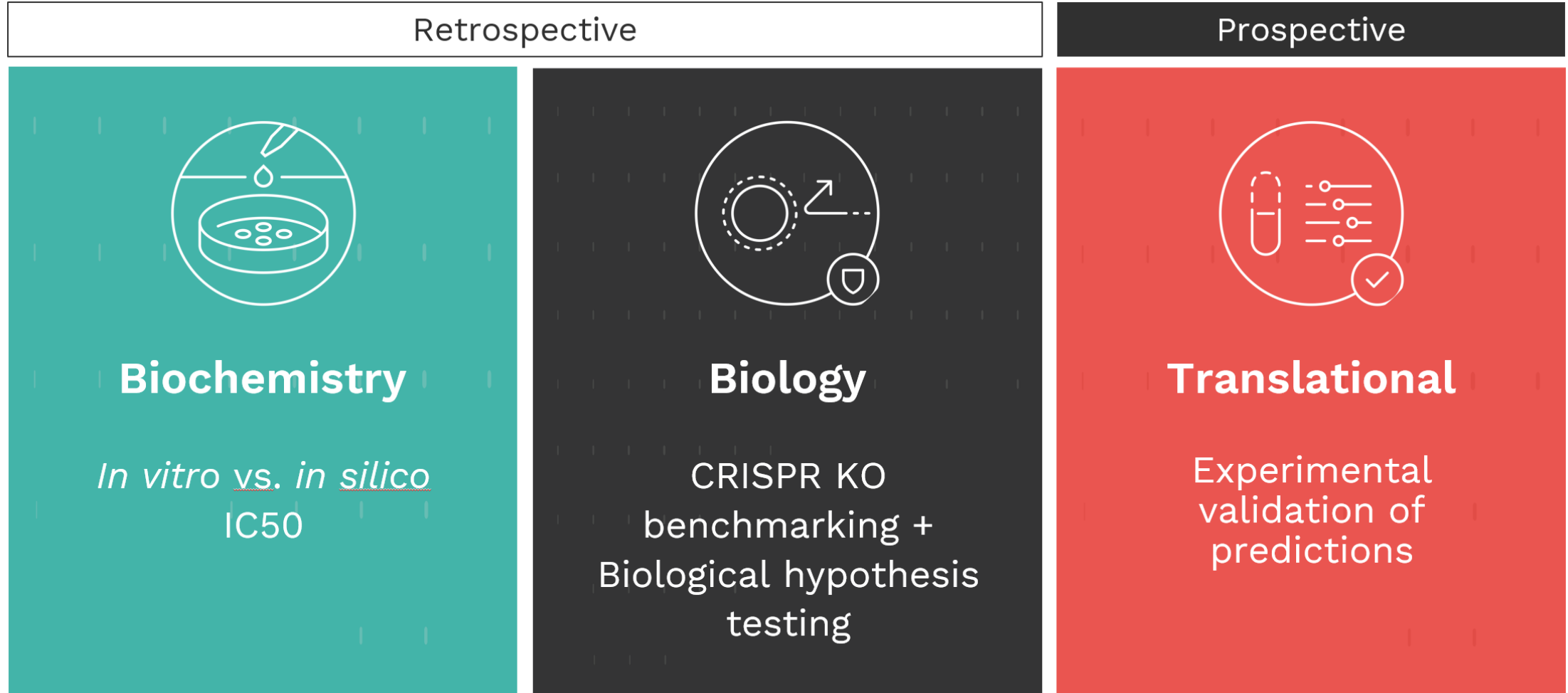
- 16) Microtubule dynamics
- 17) NFKB
- 18) Notch
- 19) p38/JNK
- 20) PKA
- 21) PLC
- 22) Proliferation
- 23) Proteostasis/Akt/mTOR/
- 24) RTK signaling
- 25) Steroid signaling
- 26) TGFB
- 27) Toll-like receptor signaling
- 28) VEGF
- 29) WNT



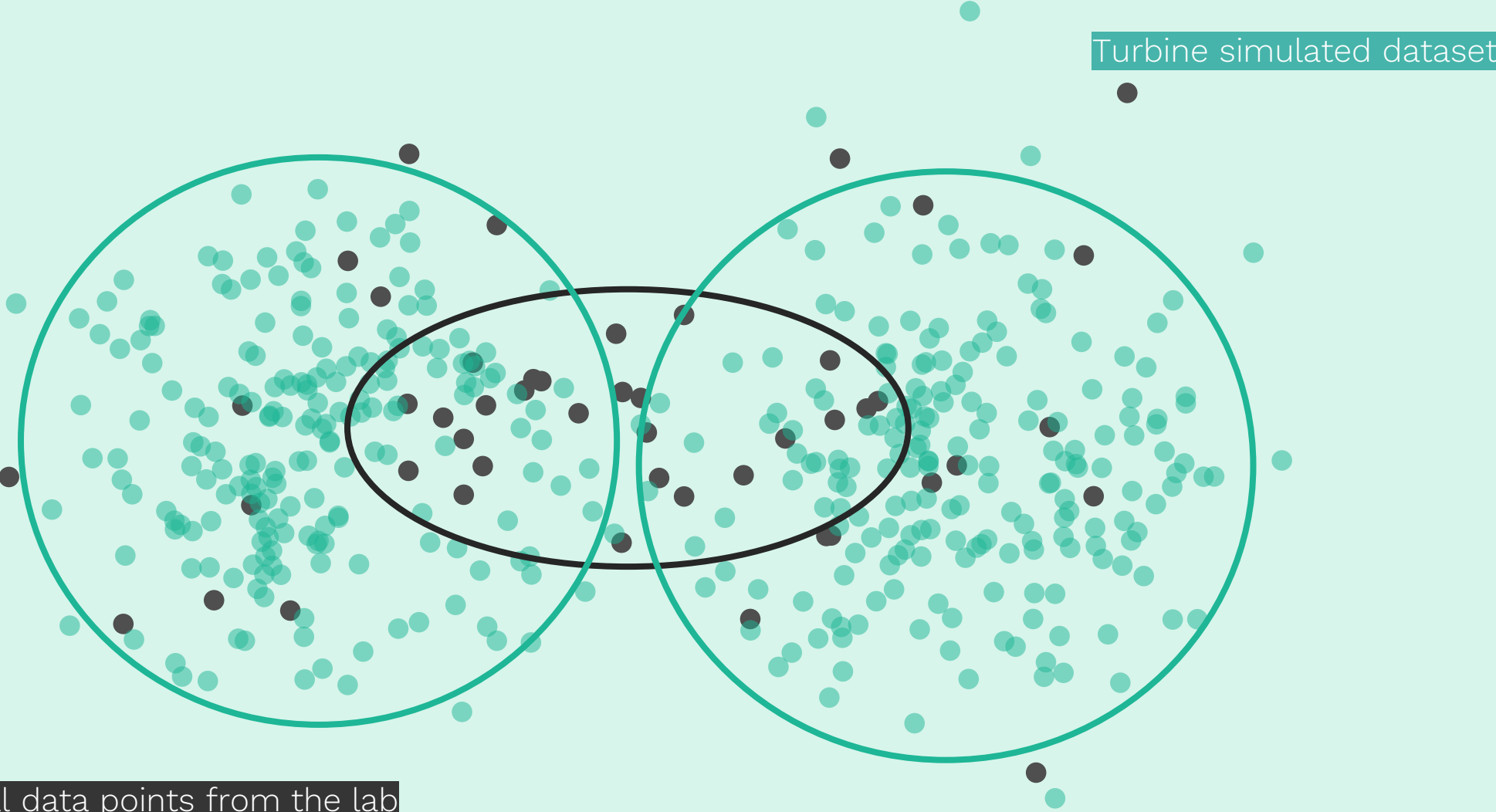
Modelling of phenotypic behavior



Three steps of validation



Interpretation by biologists and AI



Turbine simulated dataset

Experimental data points from the lab

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



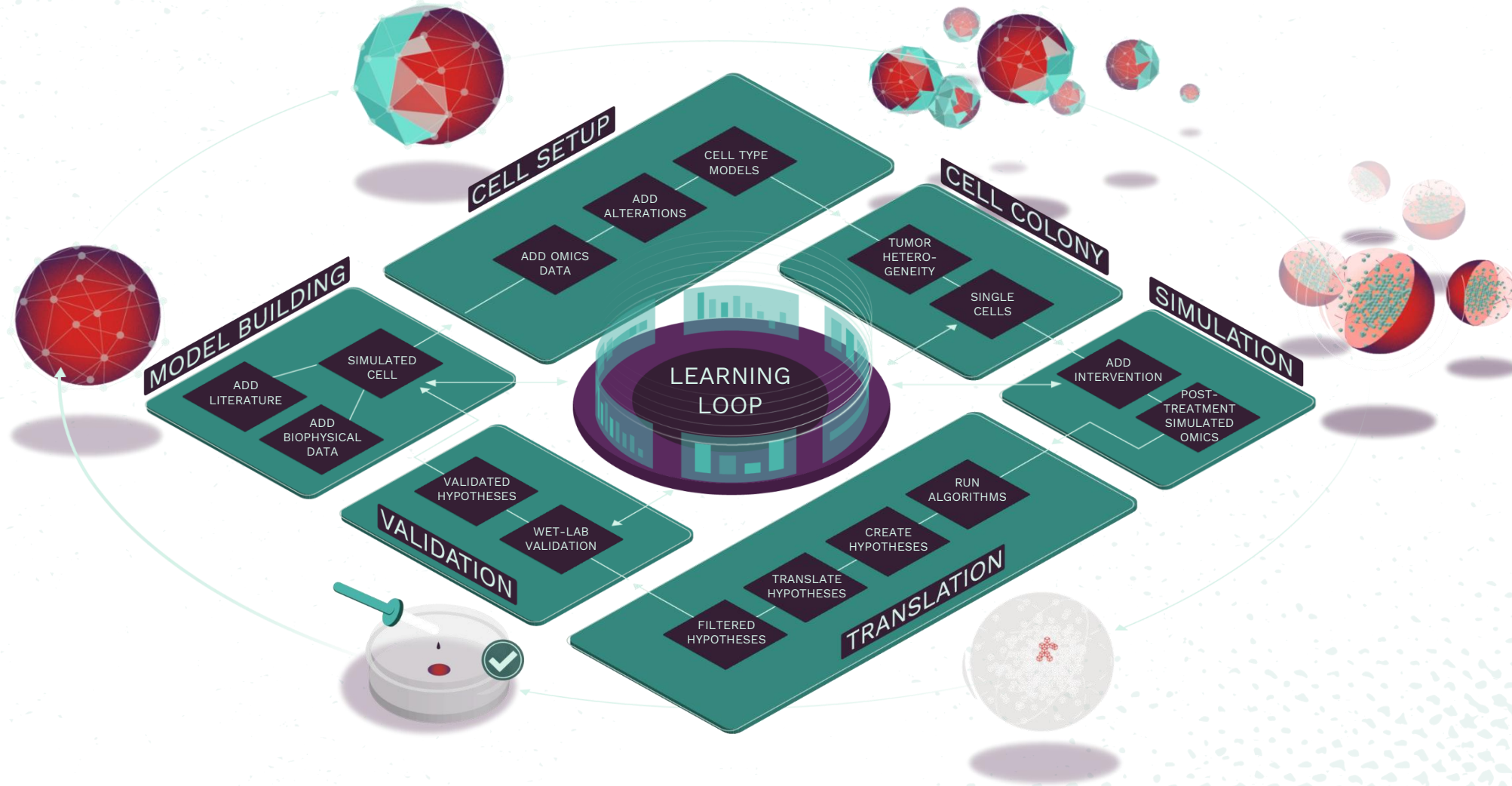
Key features of the Simulated Cell

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

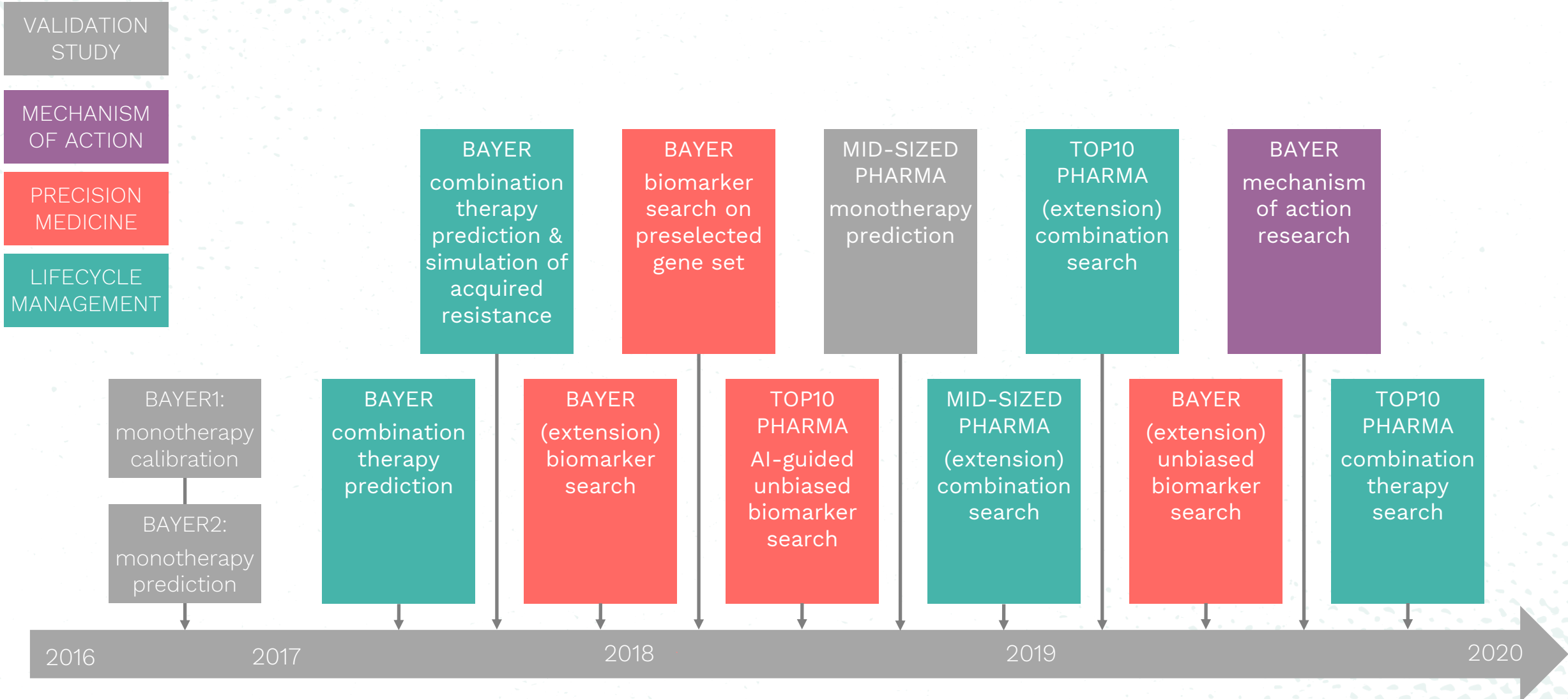
- 200+ patients' data
- 611 cell lines
- 185 drugs in monotherapy and combinations





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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.

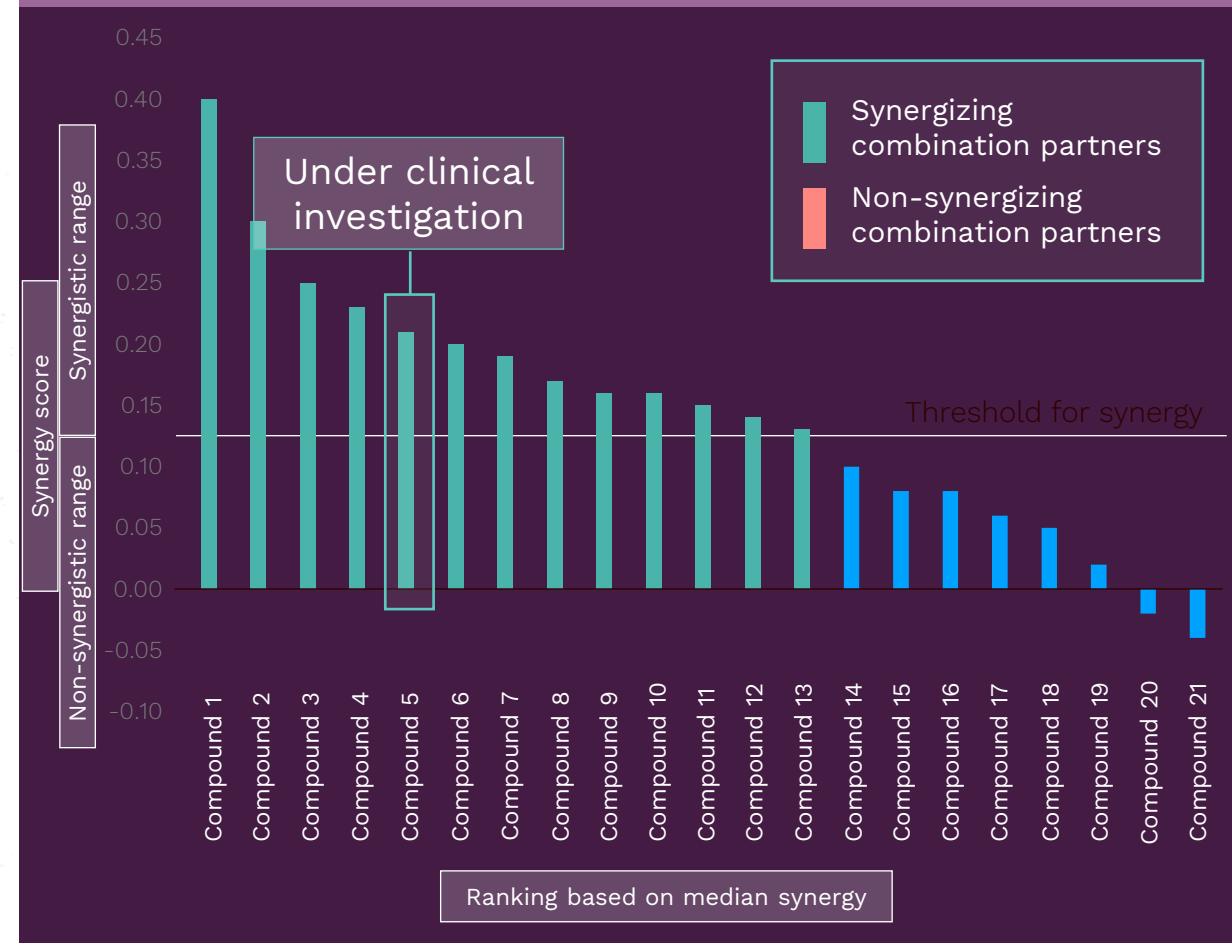
Expanding the indications

- 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***.

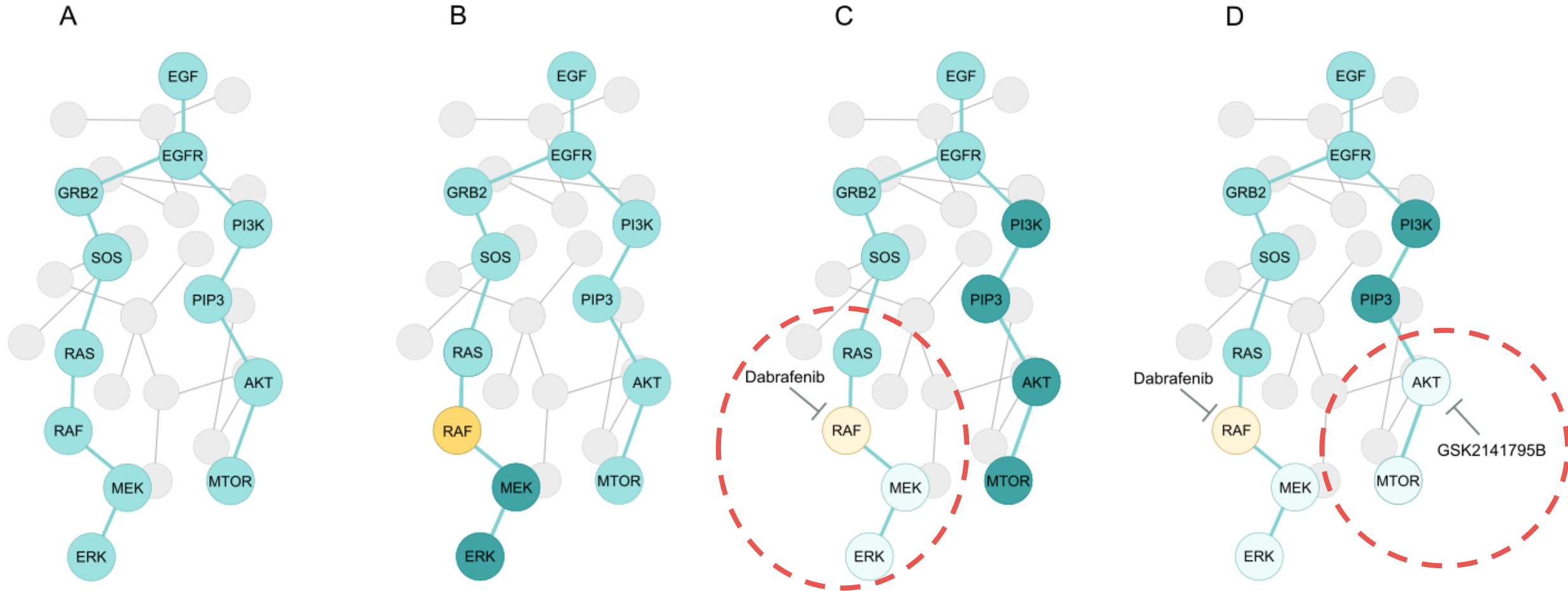
Outcome

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

Combination screen of 21 potential combination partners



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

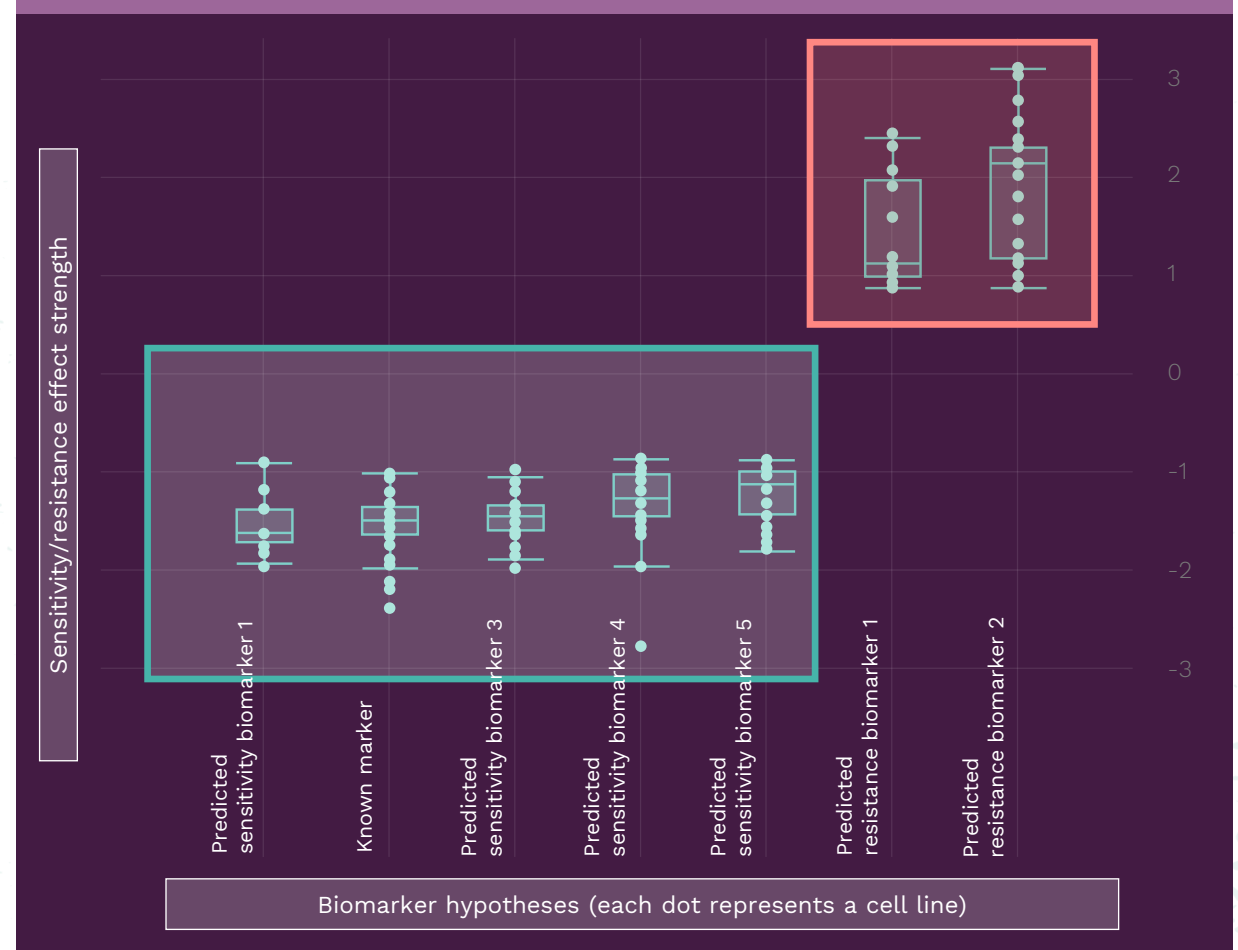
The process

- 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

Effect strength distribution of highlighted biomarker hypotheses

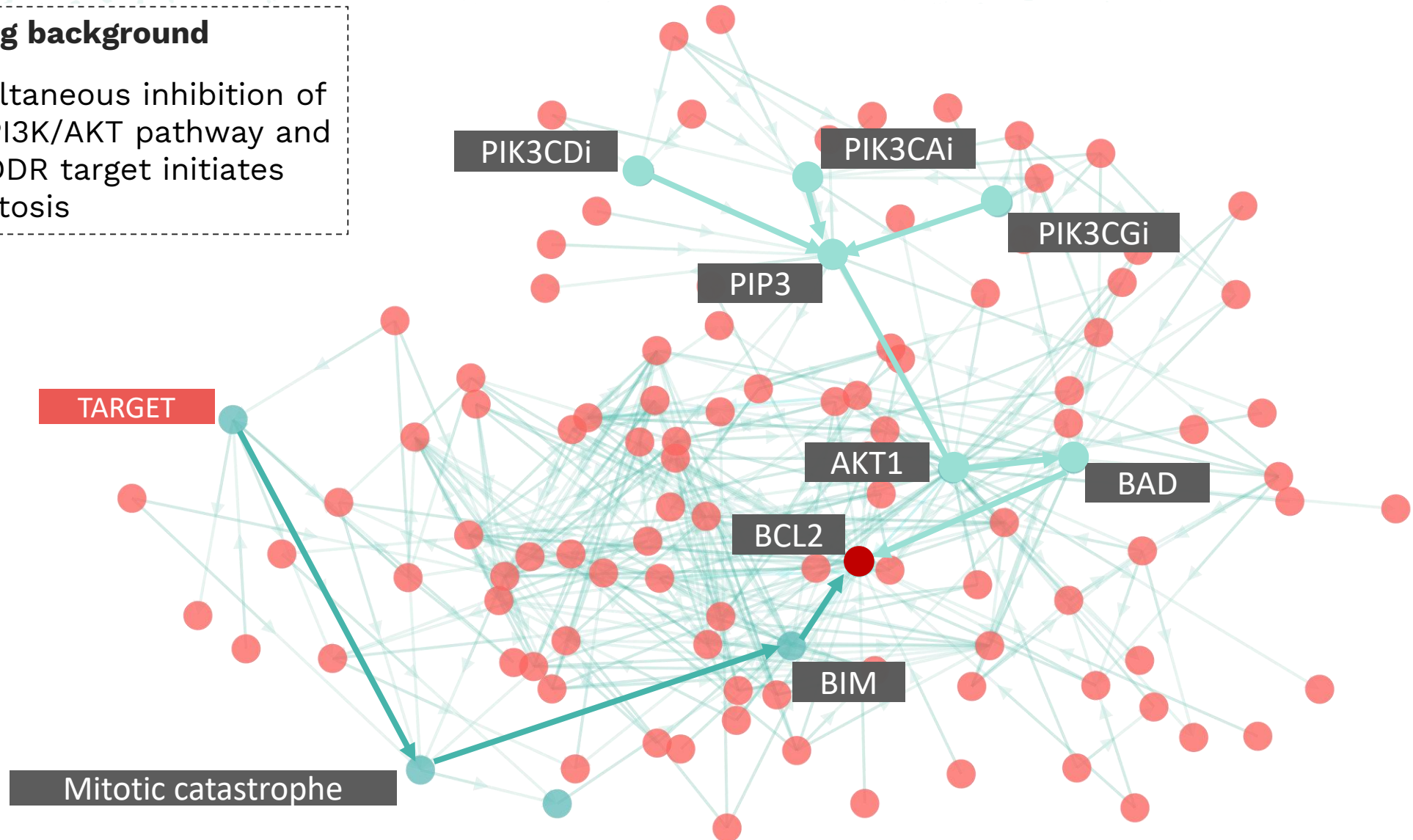


Network strategy to find non-trivial biomarkers



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.

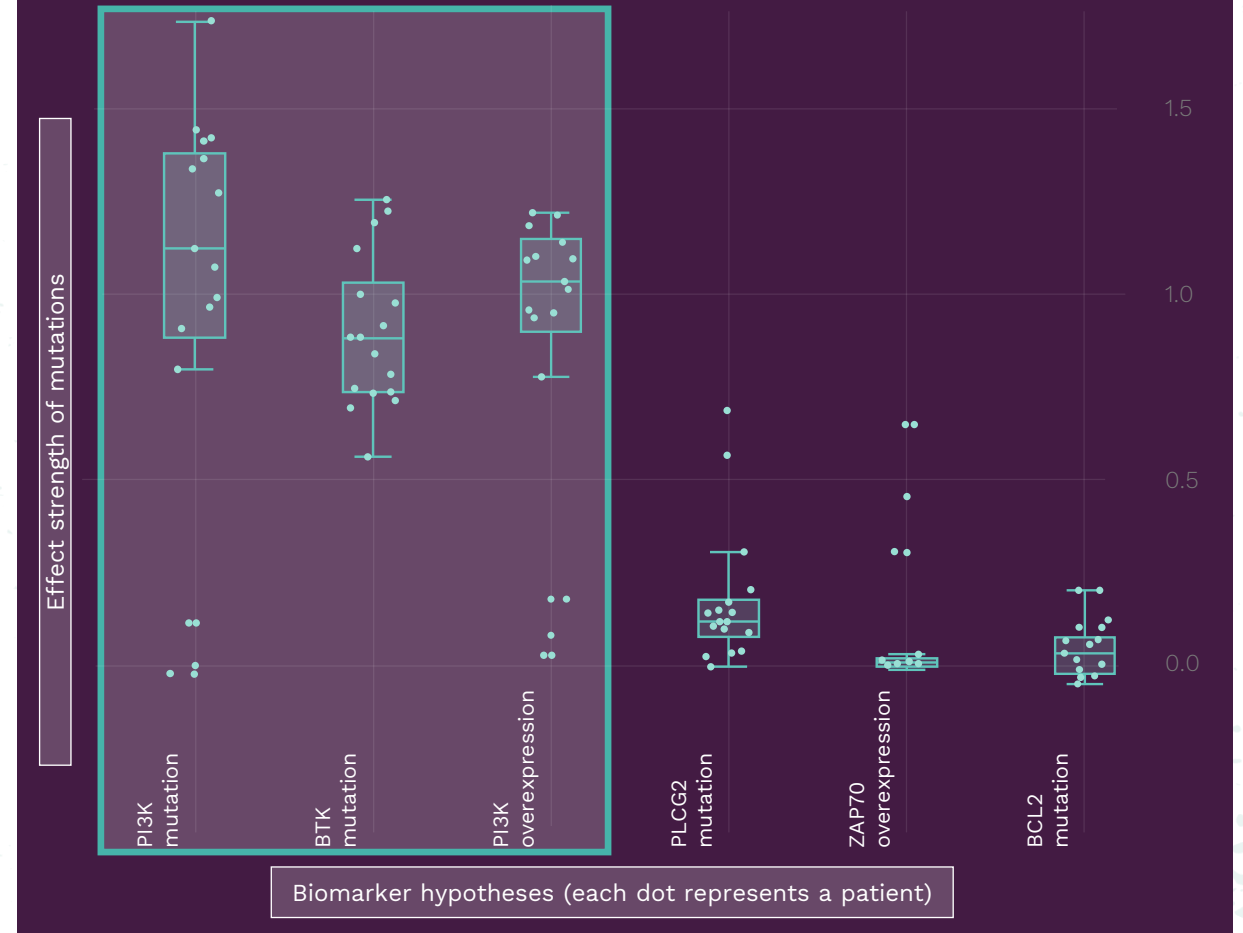
Understanding the disease mechanism

- 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.**


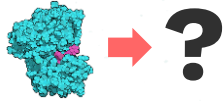
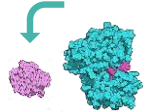
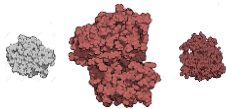
Analysis of *simulated* molecular alterations leading to resistance



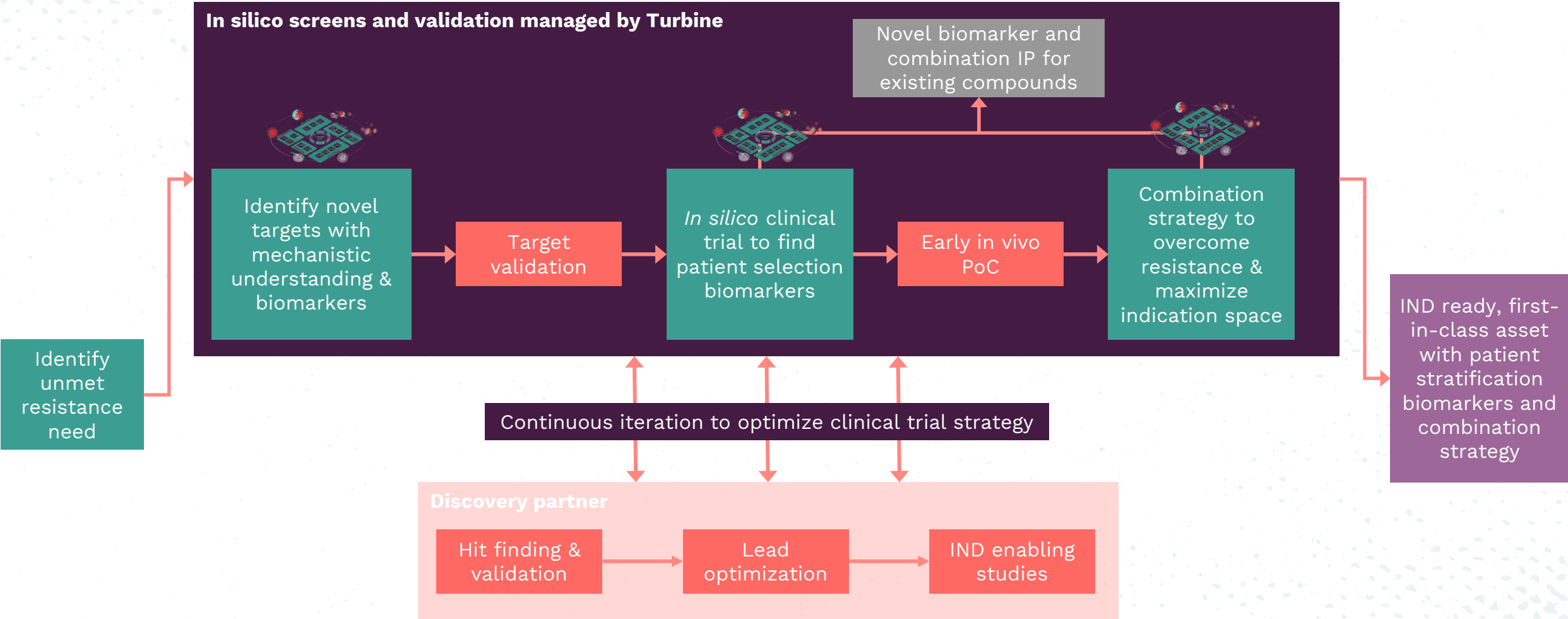
Turbine advantages in finding novel cancer targets compared to CRISPR



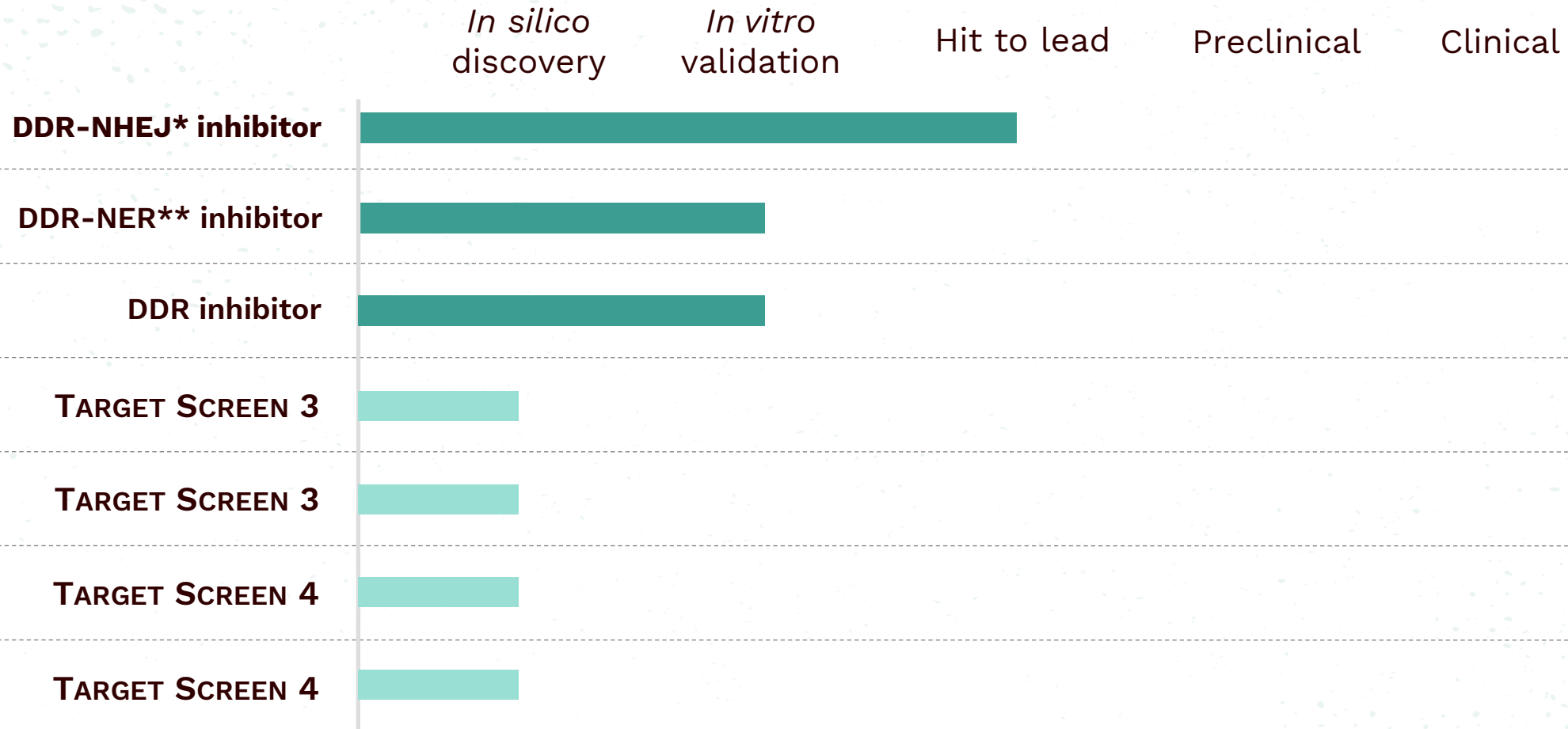
CRISPR overlooks several mechanisms driving cell behaviour and the evolutionary pressures leading to resistance. In comparison, the Simulated Cell™ takes a holistic view of the cell and deploys cell behaviour simulations to quickly reveal the potential of the targets' clinical relevance.

	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-deficiency 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

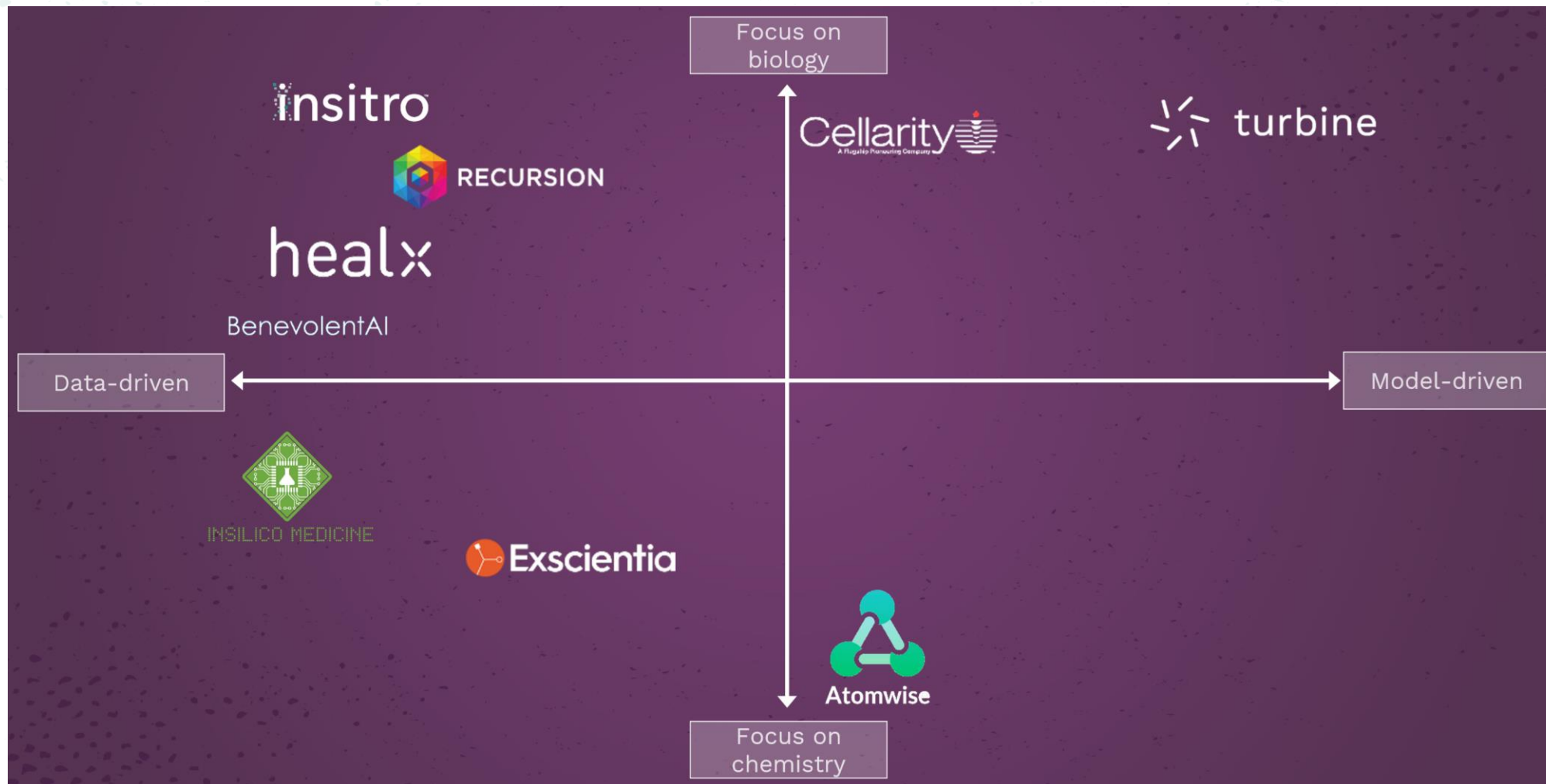


* Non-homologous end joining
** Nucleotide excision repair



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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

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