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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Initial patent filed</td>
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<tr>
<td>2</td>
<td>Hit finding phase</td>
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<tr>
<td>4</td>
<td>Targets tackling PARPi resistance</td>
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#### Predictions validated in clinical trials

- 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
- Delin

#### 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

<table>
<thead>
<tr>
<th>Preinvasive cancer</th>
<th>Ductal</th>
<th>Lobular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cells limited to basement membrane</td>
<td>Ductal carcinoma in situ (DCIS) 80% May spread through ducts and distort duct architecture 1% progress to invasive cancer per year Usually unilateral</td>
<td>Lobular carcinoma in situ (LCIS) 20% Does not distort duct architecture Some genetic abnormality as ILC – E-cadherin loss 1% progress per year Can be unilateral</td>
</tr>
</tbody>
</table>

| Invasive cancer | 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 IDC precursor Minimal fibrous response, presents less often with palpable mass Metastasis through abdominal viscera to GI, ovaries, uterus Almost always ER+ |

<table>
<thead>
<tr>
<th>Molecular subtypes</th>
<th>Triple negative</th>
<th>HER2+</th>
<th>Luminal B</th>
<th>Luminal A</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of breast cancers</td>
<td>15-20%</td>
<td>10-15%</td>
<td>20%</td>
<td>40%</td>
</tr>
<tr>
<td>Receptor expression</td>
<td>HER2</td>
<td>ER+/PR+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histologic grade</td>
<td>High (grade III)</td>
<td>Low (grade I)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prognosis</td>
<td>Poor</td>
<td>Good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response to medical therapy</td>
<td>Chemotherapy</td>
<td>Trastuzumab</td>
<td>Endocrine</td>
<td></td>
</tr>
</tbody>
</table>

*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.*

Sources:

- Clin Transl Oncol. 2008 Dec; 10(12): 717-23
- Nat Clin Pract Oncol. 2007 Sep; 4(9): 514-25
Advancements in molecular diagnostics leads to the fragmentation of cancer indications

“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
Examples for indication-agnostic targeted therapy

No. patients

Diagnostic challenge

NTRKi

PARPi

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

Key gaps filled by understanding underlying biology

Relevant target

First patient to dose

Patient response

Overcoming resistance

Sources:
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

1. Simulated Cell model
2. Modelling of phenotypic behavior
3. 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 signaling
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) JAK/STAT
14) NFkB
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
30) TGFB
Modelling of phenotypic behavior
## Three steps of validation

<table>
<thead>
<tr>
<th>Retrospective</th>
<th>Prospective</th>
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</thead>
<tbody>
<tr>
<td><strong>Biochemistry</strong></td>
<td><strong>Translational</strong></td>
</tr>
<tr>
<td><em>In vitro vs. in silico</em>&lt;br&gt;IC50</td>
<td>Experimental validation of predictions</td>
</tr>
<tr>
<td></td>
<td>CRISPR KO benchmarking + Biological hypothesis testing</td>
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</table>
Interpretation by biologists and AI

Experimental data points from the lab

Turbine simulated dataset
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

Mitotic catastrophe

TARGET

PIK3CDi
PIK3CAi
PIK3CGi
PIP3
AKT1
BAD
BCL2
BIM

26
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.
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.

## Turbine advantages in finding novel cancer targets compared to CRISPR

<table>
<thead>
<tr>
<th>1. Precision Targeting</th>
<th>CRISPR Limitations</th>
<th>Drug Discovery (Dis)Advantage</th>
<th>Turbine Advantage</th>
<th>Turbine Proof</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Knocks out the entire gene</td>
<td>Pharmacological inhibitors may have different phenotypic effect, gene product may be undruggable</td>
<td>Simulate partial inhibition functional KO to reveal viable targets, identify alternative, druggable targets with similar phenotypic effect</td>
<td>We identified ATR as a promising target, as opposed to DepMap which considers it toxic due to its common essentiality</td>
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| 2. Durability | 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 |

| 3. Translatability | 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 |

|                       | 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.

**In silico screens and validation managed by Turbine**

- Identify novel targets with mechanistic understanding & biomarkers
- Target validation
- *In silico* clinical trial to find patient selection biomarkers
- Early in vivo PoC
- Combination strategy to overcome resistance & maximize indication space

Novel biomarker and combination IP for existing compounds

Continuous iteration to optimize clinical trial strategy

**Discovery partner**

- Hit finding & validation
- Lead optimization
- IND enabling studies

IND ready, first-in-class asset with patient stratification biomarkers and combination strategy
Continuous development of the Simulated Cell enables novel target screens, leading to the expansion of our pipeline.

<table>
<thead>
<tr>
<th>DDR-NHEJ* inhibitor</th>
<th>In silico discovery</th>
<th>In vitro validation</th>
<th>Hit to lead</th>
<th>Preclinical</th>
<th>Clinical</th>
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<tr>
<td>DDR-NER** inhibitor</td>
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<tr>
<td>DDR inhibitor</td>
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<td>** TARGET SCREEN 3**</td>
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<td>** TARGET SCREEN 3**</td>
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* 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
Véleményezés QR-kód-AOK
report.semmelweis.hu/pin PIN-kód AOK: KZ3

Véleményezés QR-kód-FOK
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