Targeted Therapeutics for Cancers With Gene Amplification

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The Problem: many cancer targets are “undruggable”

1. Amplified Cancer Driver Genes

Gene amplification is a critical factor driving major oncogenic processes:

- Cell Proliferation
- Angiogenesis
- Decreased Apoptosis
- Migration and Invasion

2. Current Treatment Strategy:
   Target the Overexpressed Protein Product

Major drug breakthroughs in oncology have targeted the proteins encoded by amplified genes:

- **Herceptin**, antibody targeting the HER2 receptor, treats HER2-positive breast cancers
- **Gefitinib**, small molecule tyrosine kinase inhibitor directed against EGFR, central in lung cancer therapy.

3. The problem with the current approach

- Protein overexpression is a requisite for activity
- Many proteins are undruggable by small molecules
- Primary and acquired resistance
Our Approach: directly target the amplified DNA

...and manipulate the DNA Damage Response Network to trigger apoptosis in cancer cells

1. Novel Treatment Strategy

Develop a drug platform that directly converts amplified oncogenes to excessive DNA damage which activates apoptosis

2. Advantages of hijacking the cell’s own machinery

- Reduces normal tissue toxicity and off-target effects
- Independent of protein cellular function
Our Solution: DIOs as anticancer therapeutic strategy

- **DIOs**: damage-inducing oligonucleotides
- **Molecular target**: polypurine sites in the amplified cancer genes
- **MoA**: sequence-specific gene targeting and generation of DNA damage to induce p53-independent apoptosis in cancer cells
- **POC**: HER2-positive breast cancer, a well characterized gene amplified cancer with established cell and animal models.
- **IP portfolio of three patents**:
  - Granted: US9587238B1 “Gene-targeted apoptosis”
  - Pending: 1 additional
We designed HER2-205 to target a polypurine sequence in the HER2 gene and demonstrated in vitro that:

- Level of induced DNA damage correlates with gene copy number
- Increase in apoptosis is proportional to an increase in HER2 gene copy number
- Induction of apoptosis via a p53-independent apoptotic pathway

The Rogers lab unpublished data: manuscript in revision at Nature Biotechnology
Our Initial POC Molecule: HER2-205

**HER2-205 in vivo bioactivity:**

- HER2-205 treatment has performed on par with Herceptin in human breast tumor xenografts
- HER2-205 is a feasible therapeutic alternative for drug resistant breast and ovarian cancers with copy number gains

**HER2-positive Breast Cancer Model**

**HER2-positive Ovarian Cancer Drug Resistant Model**

The Rogers lab unpublished data: manuscript in revision at *Nature Biotechnology*
## HER2 Targeted Therapeutics: competitors and differentiating benefits

<table>
<thead>
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<th>TargetGene Therapeutics</th>
<th>SILVERBACK Therapeutics</th>
<th>Roche</th>
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<tbody>
<tr>
<td>Gene Targeting</td>
<td>Yes</td>
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<tr>
<td>Healthy Tissue Toxicity</td>
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<td>Protein Targeting</td>
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<td>Specificity</td>
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<td>Preclinical/Clinical</td>
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<td>Total Raise or Market Cap</td>
<td>To be determined</td>
<td>$211M (Series A-C)</td>
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Our Vision: a broadly applicable novel drug platform

**Multiple cancer types can be targeted with our DIO approach**

- 519, 971 unique DIO targeting sequences throughout the human genome
- **Gene Families**
  - 461 amplified genes
  - 14 cancer subtypes
  - Epigenetic regulators
  - Cell cycle-associated genes
  - DNA damage response

**Our Ultimate First Indication:**
*High-Grade Serous Ovarian Cancer (HGSOC)*

Genomic landscape of **high-grade serous ovarian cancer** is characterized by:
- prevalent p53 mutations (96% of patients)
- widespread gene amplification (20-30% of patients)
- absence of oncogenic point mutations

- **Brain**
  - EGFR
  - MYC
  - PDGFR
  - MET
  - KIT

- **Breast**
  - ERBB2
  - PIK3CA
  - MYC
  - GRB7
  - ERCC5

- **Melanoma**
  - BRAF

- **Ovarian**
  - ERBB2
  - KRAS

- **Gastric**
  - OCT1
  - PIK3CA
  - MET
  - EGFR
  - MYC
  - FGFR2
  - ERBB2

- **Colorectal**
  - BRAF
  - KRAS
  - ERBB2
## Blavatnik Funds: Proposed Studies and Timeline

### Therapeutic Targeting of Gene Amplification in HGSOC

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<thead>
<tr>
<th>Month</th>
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<td>DIO Design (4 programs) $40K</td>
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<td>In vitro validation of DIOs $50K</td>
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<td>Scale-up Production of Lead DIO $100K</td>
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### Phase I: Design and Evaluation of Bioactivity
- Design DIOs to target genes amplified in HGSOC
- Target genes: CCNE1, MYC, PIK3CA, NOTCH
- Milestone: Identification of 2-3 lead DIOs that induce gene copy number dependent apoptosis
- **Timeline:** Months 1-6

### Phase II: Determination of Therapeutic Efficacy
- Develop delivery platform (antibody, nanoparticles)
- Establish *in vivo* PK and biodistribution of DIOs
- Determine normal tissue toxicity
- Evaluate anticancer activity in human ovarian models
- **Timeline:** Months 6-12