Targeting Cancer with a Novel Antibody Drug Conjugate

**PI:** Lajos Pusztai, M.D., D.Phil.
Professor of Medicine, Director of Breast Cancer Translational Medicine,
Co-Director of the Genetics and Genomics Program,
Yale Cancer Center
Apeiros Team

Lajos Pusztai, MD, DPhil. Role: PI
- Two decades of experience in laboratory and translational research
- Principal investigator of several Phase I, II and III trials and internationally recognized clinical trialist.
- Chair NCI-SWOG Breast Committee
- Inventor of several patents (http://patents.justia.com/inventor/lajos-pusztai)
- Published over 300 manuscripts in high impact medical journals

Daryl E Klein, MD, PhD Role: Co-PI
- Leads the Fab discovery phage display program at the Yale Cancer Biology Institute
- Expert in protein production and structural biology

Jamison Langguth, MSED, MPH Role: Business Development
- 8 years of clinical trials operations experience (4 years in oncology)
- Co-founder, Aero Therapeutics
- Management degree from Harvard
- Current Blavatnik Fellow in Life Science Entrepreneurship at Yale

David Lewin, PhD Role: IP Management / Advisor
- 14 years of licensing and marketing experience in life sciences
- >20 years successfully managing scientific-based business alliances with pharmaceutical leaders in the U.S., Europe and Japan.
The continued challenge of cancer

In 2019, cancer deaths overtook cardiovascular deaths in many industrialized countries. (Dagenais et. al. Lancet, Sept 03, 2019)

Antibody drug conjugates (ADC):
1. Cancer-targeting reduces adverse effects
2. Allows delivery of highly effective toxins
3. Favorable efficacy / toxicity profile
4. Several notable success stories
5. Past failures to learn from

Our goal is to generate a novel drug, humanized anti-GABRP antibody that is conjugated to DM1 (or similar cytotoxic cargo) to treat cancers that express high levels of the GABRP receptor.
**A novel ADC target**  
GABRP; gamma amino butyric acid receptor pi subunit

**Panel A:**  
- GABRP mRNA is an aberrantly expressed cell surface receptor subunit, high in breast, lung, gastric, pancreatic, ovarian and colorectal cancers.  
- Low in normal tissues.

**Panel B:**  
- GABRP protein can be detected by immunohistochemistry in subsets of breast cancer

**Panel C:**  
- GABRP protein is expressed in the cell membrane

Proof of principle functional studies
GABRP gene knockdown and anti-GABRP antibody impair cell viability

Panel A:
- GABRP knock-down cells show impaired growth in mice xenografts.

Panel B:
- Naked anti-GABRP extracellular domain (ECD), but not intracellular (ICD) domain, targeting antibody inhibits cell growth in vitro

Panel C:
- Anti-GABRP (ECD) conjugated to DM1 toxin inhibits cell growth in all 5 GABRP+ cell lines in vitro


Confidential, not for distribution
Generation of a series of proprietary antibody fragments (FAB) to target GABRP

In vitro binding of FABs to GABRP using ELISA

FAB binding to GABRP expressing MD-MB468 cells using flow cytometry

Naked anti-GABRP FABs inhibit cell growth in vitro

Patent Pending

“Anti-GABRP Antibodies and Fragments Thereof, Conjugates Comprising Same, and Methods of Use”
ADC Market Size in TNBC alone by 2024

Target:
20% of TNBC Market

$1.2 B
$6.3 B
$31 B

Breast Cancer
Total Market

TNBC Breast

Future Potential Indications:
Lung, Gastric, Pancreatic, Ovarian and Colorectal.
Competitive Landscape

<table>
<thead>
<tr>
<th>Other name</th>
<th>Immunomedics</th>
<th>Seattle Genetics</th>
<th>Celldex</th>
<th>Sanofi</th>
<th>Pfizer</th>
<th>Pfizer</th>
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<tbody>
<tr>
<td><strong>Immunomedics</strong></td>
<td>Sacituzumab Govetican / IMMU-132</td>
<td>Ladiratuzumab vedotin / SGN-LIV1A</td>
<td>Gl embatumumab vedotin / CDX-011</td>
<td>SAR566658</td>
<td>cof etuzumab / PF6647020</td>
<td>PF6647263</td>
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<tr>
<td><strong>Target</strong></td>
<td>Trop-2</td>
<td>LIV-1</td>
<td>gpNMB</td>
<td>CA6</td>
<td>PTK7</td>
<td>EphA4</td>
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<tr>
<td><strong>Tumor expression</strong></td>
<td>88%</td>
<td>71%</td>
<td>40%</td>
<td>UNK</td>
<td>29%</td>
<td>UNK</td>
</tr>
<tr>
<td><strong>Cytotoxin</strong></td>
<td>SN-38</td>
<td>MMAE</td>
<td>MMAE</td>
<td>maytansinoid DM4</td>
<td>auristatin-0101</td>
<td>Enediyn/DNA</td>
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<tr>
<td><strong>Single-agent activity (ORR)</strong></td>
<td>35%</td>
<td>27%</td>
<td>18%</td>
<td>13%</td>
<td>20%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Registrational trials</strong></td>
<td>ASCENT ≥3rd line</td>
<td>Active arm in ISPY-2; Phase II trial 2018</td>
<td>METRIC; 1st-3rd line; Same as Capecitabine</td>
<td>Phase II</td>
<td>Phase II</td>
<td>Phase I</td>
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**FDA approved ADCs (2019):**
1. Ado-trastuzumab emtansine (TDM1) for HER2 positive Breast Cancer
2. Brentuximab vedotin for CD30 positive Hodgkin’s lymphoma
3. Gemtuzumab ozogamicin for CD33 positive Acute Myeloid Leukemia

Kadcyla™ worldwide sales 914 million USD in 2018.
1. We have:
   - Identified a novel target that is high in cancers low in normal tissues and developed a detection assay
   - Demonstrated proof-of-principle functional importance and inhibitory effect by naked antibody and ADC
   - Generated proprietary FABs and secured initial IP

2. Next steps to IND
   - Affinity maturation and generation of a full length humanized anti-GABRB antibody.
   - Custom conjugation to cytotoxic cargo (i.e. DM1, exatcain, SN38) and characterization of cytotoxic effect in vitro and in vivo.
   - GMP production, pre-clinical PK and toxicity studies

3. Phase I/II clinical testing
   - Intimal focus on TNBC in the neoadjuvant and first/second line metastatic space
Timeline to the clinic

- **Affinity Maturation**
- **Generation of a fully humanized antibody**
  - **IND-Enabling Work**
    - $150K
    - 1). Custom conjugation of the humanized anti-GABRP antibody to cytotoxic cargo emtansine (i.e. DM1, exatican, SN38).
    - $150K
    - 2). Characterize cytotoxic effect of the affinity matured FABs, humanized anti-GABRP antibody and anti-GABRP-ADC in vitro and in vivo.
- **Build Aperios Core Team**
- **CMC Formulation**
- **IND**
- **Phase I Clinical Trial**

- **$500K Breast Cancer Research Foundation**
- **Grant Funding**
- **$300K Blavantik**
- **$5M Series A**