Novel treatment strategies for triple negative breast cancer (and other epithelial cancers)

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ASDERA – Overview

**Mission**

**Goal:** To bring novel drugs to market for high unmet needs.

**Approach**

**How:** Derisking and finding targeted therapies through a computational biostatistics platform (US 7,664,616),

**Advantage:** the first to identify genetic risk factors for complex diseases

**Time-Pipeline**

- **Validation:** Confirmation of known drug targets in epilepsy
- **PoC:** L-fucose in Crohn’s disease (in phase 3)
- **Out-licensed:** ASD-002 against mutism in autism (phase 3 ready)
- **Current lead:** ASD-003 against breast cancer metastases (pat. pending)
- **Outlook:** Delaying Alzheimer’s and Parkinson’s (pat. pending)
### ASDERA – Overview

**Derisking**

**How:** Finding targeted therapies through a computational biostatistics platform (US 7,664,616), **Advantage:** the first to identify genetic risk factors for complex diseases

**Drug Discovery Platform (US 7,664,616)**

The platform screens not only for individual genetic ‘letter’ positions (SNPs) but genetic ‘words’ (several neighboring SNPs).

It also accounts for genetic ‘grammar’ (neighborhood, compound heterozygosity, recombination hotspots, ...) **within the statistical method.**

Feasible only since 2001 (32-bit OS), it already yielded several hits.

**Methodology based on Technology**

<table>
<thead>
<tr>
<th>Year</th>
<th>Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1800</td>
<td>Gauss-Legendre</td>
</tr>
<tr>
<td>1900</td>
<td>Ohdner 9 Byte ANOVA</td>
</tr>
<tr>
<td>1865</td>
<td>IBM 256 kB PCA</td>
</tr>
<tr>
<td>1985</td>
<td>PC 16 MB Bayes</td>
</tr>
<tr>
<td>1948</td>
<td>Hoeffding</td>
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<tr>
<td>2001</td>
<td>GPU 4 GB u-Stat</td>
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### ASDERA – Market Need / Opportunity

**Breast cancer**

Breast cancer (BC) is the most common cancer in women worldwide. 250,000 new US cases per year, to a prevalence of ~5,000,000 in the US.

**Triple-neg. Breast Cancer**

US: 37,500/yr are triple negative (TNBC, 15% of breast cancer)
- high risk of distant metastases after surgery (20% at 2.5 yr) \cite{Dent 2007}
- high risk of death median time to death (13% at 2.5 yr)

**Unmet Need BC**

Most breast cancer death are caused by metastases, yet no targeted treatment exists to prevent metastases.

**Unmet need TNBC**

For TNBC, the only treatment options after surgery have severe side effects:
- radiation
- chemotherapy
ASDERA’s Novel Discovery Technology and α-cyclodextrin Hit

**Discovery Platform**
Analyzed 3 independent breast cancer populations
 Generated consistent results, which suggested a Novel treatment concept

**Genetic results**
Results showed metastases are associated with
• variations along the endo-/exocytosis (EEC) pathway
• variations in the PI cycle, which regulates EEC.

**Independent Confirmation**
“Derailed endocytosis” is a known component of BC etiology.
Of the 27 EEC genes identified, 24 have known function in BC.
4 additional EEC/BC genes had been identified in other GWAS.
16 additional EEC/BC genes had been identified in functional studies.

**Mode of Action**
ASD-003 is a derivative of αCD
αCD down-regulates endocytosis by scavenging serum phospholipids

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“Derailed Endocytosis” (Mosesson 2008) of β1 Integrin in Breast Cancer

(adopted from (Mosesson 2008) and (De Franceschi 2015))
ASDERA – Consistent Gene Families Across Three Studies

Genes significant in muGWAS (s6) / ssGWAS (s1) (Genes significant in previous GWAS of first study boxed)

Membrane associated (GPCR, FcR, HA, RTK, Ion channels), incl. FGFR2

MAP Kinases

Nuclear processes (cell cycle control, transcription, splicing). incl. BUB3

Endo-/Exocytosis (EEC)!

Recycling of β1 Integrin by Endo- and Exocytosis (EEC) ...
... is Regulated by Phospholipids (LPA, PC, PS) Entering the PI Cycle

Pink genes associated with BC in genetic analysis.

Colored arrows sequence of PIPs involved in EEC.

Hypothesis:
Scavenging serum phospholipids "re-rails" endocytosis

Cyclodextrins scavenge Lipids

α- and β-Cyclodextrin (αCD, βCD) scavenge Phospholipids

βCD also scavenges Cholesterol

Permanent Hearing Loss

αCDₙ=6 / βCDₙ=7
ASD-003 (HPαCD*) is >2× as effective as HPβCD against migration

MCF-7 human ER+ BC cells

<table>
<thead>
<tr>
<th>Dose [mM]</th>
<th>ASD-003</th>
<th>HPβCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>80</td>
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</tr>
<tr>
<td>2</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

MDA-MB-231 human ER− BC cells

<table>
<thead>
<tr>
<th>Dose [mM]</th>
<th>ASD-003</th>
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</table>

ANOVA: p = .0252

ASDERA – *in vitro*/Animal Evidence for Efficacy of bCD

**In vitro**
- βCD reduces migration of human BC cells [Raghuv 2010, Guerra 2016]
- αCD is >2× as effective as βCD in two BC cell lines (p=.0252)
- => βCD acts by scavenging PLs (like αCD) not by scavenging cholesterol

**ex vivo**
- βCD inhibits angiogenesis in chick embryo and rat aorta assays, but not by altering cell proliferation [Watson 2013]

**in vivo**
- βCD, in mice implanted with human tumor cells,
  - reduces tumor volume from MCF-7 BC and A2780 OC cells [Grosse 1998]
  - reduces lung metastases from H7-O Lewis lung cancer cells [Zhang 2006]
  - reduces invasion of melanoma cells [Fedida-Metula 2008]

**Clinical**
- LPA† has been linked to BC risk [Wang 2016]
- Trials of alkyl-LPCs against BC metastasis showed GI toxicity [Rios-Marco 2017]

**US approval**
- αCD is GRAS for oral use
- αCD is approved for injection (Caverject®)
## Study Design

The clinical trial(s) will be conducted in 600 women undergoing surgery for triple-negative (TN) node-positive (NP) breast cancer (BC) with ≥2 yr of follow up (FU) with a futility/IIb analysis after ≥2 yr in 120 women.

<table>
<thead>
<tr>
<th>Study Design</th>
<th>TNBC</th>
<th>Adjuvant therapy after resection</th>
<th>Disease-Free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00130533: 900 TN, NP</td>
<td>≤ 5 yr FU (capecitabine ~ placebo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00630032: 750 TN</td>
<td>≤ 5 yr FU (docetaxel : ixabepilone)</td>
<td></td>
<td></td>
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<tr>
<td>NCT00789581: 600 TN</td>
<td>≤ 5 yr FU (pactitaxel ~ ixabepilone)</td>
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<td></td>
</tr>
<tr>
<td>NCT01057069: 300 TN</td>
<td>≤ 5 yr FU (5 drugs : 2 drugs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01112826: 428 TN</td>
<td>≤ 3 yr FU (capecitabine : placebo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01150513: 320 TN</td>
<td>≤ 3 yr FU (epirubicin... ~ carboplatin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01642771: 600 TN</td>
<td>≤ 5 yr FU (capecitabine &gt; 5-fluorouracil)</td>
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<td></td>
</tr>
<tr>
<td>NCT01752686: 600 TN</td>
<td>≤ 5 yr FU (carboplatin : placebo)</td>
<td></td>
<td></td>
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<tr>
<td>NCT02441933: 850 TN, NP</td>
<td>≤ 5 yr FU (carboplatin : placebo)</td>
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<td></td>
</tr>
<tr>
<td>NCT02455141: 600 TN</td>
<td>≤ 3 yr FU (n adj from three arms)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02926196: 335 TN, NP</td>
<td>≤ 5 yr FU (avelumab : placebo)</td>
<td></td>
<td></td>
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<tr>
<td>NCT03036488: 850 TN</td>
<td>≤ 8 yr FU (pembrolizumab : placebo)</td>
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## ASDERA – IP and Market

**IP Protection**

US/EU patent for aCD derivatives, expiration 2039

**Market Exclusivity**

US: 7 years from NDA
EU: 10 years from NDA

**Market Size**

Target Population (US): 37,000 / yr TNBC × 4 yr = 148,000
TNBC: 37,000 × 4 yr × 50% × $20,000/yr = $1.5 B
R•BC: 250,000 × 10 yr × 10% × $20,000/yr = $5.0 B

**Forecasting**

5 yr to market, on market: 1st yr: $0.5 B, ..., 5th yr: $5 B

**Partnering Options**

- Licensing
- Joint Development Partnership with options for consideration:
  - Milestones
  - Royalty
  - Right-to-acquire option
  - Regional or global commercialization rights
ASDERA – Summary

### ASD-003
Proposed first drug to target metastases in BC, including triple-negative breast cancer (TNBC).

### Unmet Need
- BC is the most common cancer in women worldwide, ~2,500,000 in the US
- Most breast cancer death are caused by metastases.
- 30% of women diagnosed with early-stage BC will develop metastases.
- No treatment exists to prevent metastases
- Radiation and chemotherapy are the only options for TNBC

### Product
- ASD-003: Market-exclusive derivative of α-cyclodextrin (αCD)

### MoA
- αCD down-regulates endocytosis by scavenging serum phospholipids

### PoC
- βCD was effective in animal models, but may cause hearing loss
- αCD is twice as effective against migration, without ototoxicity

### IP Market
- Patent filed in US and EU.
- US market ~$5B/yr.

ASDERA – Frequently Asked Questions

1. **Why do you get GWAS results where others don’t?**
2. **Has the discovery platform been validated?**
Genetics of Heritable Diseases

If a disease are caused by a single genetic ‘letter’ variation (SNP), that variation is ‘selected against’ in just a few generations. Hence, most heritable diseases are ‘epistatic’. Some variations of SNPs (‘words’) cause the disease and are selected against, but the individual letters remain in the populations and recombine (no need for de-novo mutations).

Limitations of Bioinformatics Tools

Most bioinformatics tools in genetics are based on the statistical methods that were feasible in the 20th century, where memory was scarce. Hence, most GWAS are analyzed one SNP at a time and, thus, can detect only recent (de novo) mutations (‘letters’), but not the common cis-epistatic risk factors (‘words’). Others ignore the sequence of the letters (rwdo = word).

The ASDERA Discovery Platform

The ASDERA platform is based u-statistics for multivariate data, which were conceived in the 1940s, but never fully developed, because of memory constraints. Only after 2001 (32-bit OS) became it possible to extend u-statistics to incorporate genetic ‘grammar’ (letter sequence, ...) to increase power and avoid artifacts (US 7,664,616).

Result

Where others fail with 100,000s of subjects, ASDERA succeeds with 100s.

ASDERA – FAQ: Why do you get GWAS results where others don’t?

Epilepsy

In Childhood Absence Epilepsy, the platform identified all known targets of epilepsy drugs in a sample of 185 cases (compared to publicly available controls) only. (http://www.ncbi.nlm.nih.gov/pubmed/23438886)

Crohn’s Disease (CD)

In CD, the platform predicted many of the targets identified in studies of up to 70,000 subjects, in the original 1000 subjects. In addition, the platform identified two more genes involved in fucosylation, suggesting supplementing dietary L-fucose as a novel treatment for CD (phase 3 trial in progress).

Breast Cancer

As a finalist of the NCI’s U4C breast cancer challenge, the platform identified excessive influx of phospholipids into the PIP cycle as the cause for “derailed endocytosis” and, thus, a drug to regulate supply of phospholipids for the prevention of metastases. (In review, PLOS Genetics)

Phase 2/3

Since the platform can find the “missing heritability” in samples of 100s of subjects only, it can identify genetic risk factors for non-response in phase 3 clinical trials.

ASDERA – FAQ: Has the drug discovery platform been validated?