## ASDERA – Overview

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<th>Mission</th>
<th>Goal: To bring novel drugs to market for <strong>high unmet needs</strong>.</th>
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<td>Advantage: the first to identify genetic risk factors for <strong>complex diseases</strong> (“missing heritability”)</td>
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## ASDERA – Market Need / Opportunity (Metastatic Cancer)

| Breast cancer | Breast cancer (BC) is the **most common cancer in women** worldwide.
US: ~5,000,000 prevalence (250,000/yr). |
| --- | --- |
| Triple-neg. Breast Cancer | 37,500/yr are triple negative (TNBC, 15% of breast cancer)
• high risk of metastases post surgery (20% at 2.5 yr) \[^{[Dent 2007]}\]
• high risk of death (13% at 2.5 yr) |
| Unmet Need BC | Most cancer death are caused by metastases driven by β1 integrin, yet no targeted treatment exists to prevent metastases to brain, lung, liver, and bone. |
| Unmet need TNBC with high risk | For TNBC, the only treatment options after surgery have severe side effects:
• radiation
• chemotherapy |


## ASDERA – Market Need / Opportunity (Neurodegeneration)

| Alzheimer’s Parkinson’s | Alzheimer’s is the **most common form of dementia** worldwide (60–80%).
5,500,000 US people are affected with Alzheimer’s (AD).
1,000,000 US people are affected with Parkinson’s (PD). |
| --- | --- |
| Unmet Need AD/PD | There is no effective treatment for AD.
PD Patients often respond initially to L-dopa, but become refractory |
| Early stage Parkinson’s | Of 60,000 US people diagnosed per year, 4% (2,400) are <50 years old.
• GBA-associated PD causes 31 vs 21% dementia.
• GBA-associated PD progresses faster. |
| Unmet need Early PD with high risk | No specific treatments for GBA-PD are available. Fast progression shortens trial duration. |
ASDERA – Market Need / Opportunity (Atherosclerosis)

Coronary Artery Disease

About 92M Americans are living with a cardiovascular disease / had stroke. More people die of cardiovascular diseases, than of all cancers combined.

Risk factors

Risk factors for coronary artery disease (CAD) are
• recent myocardial infarction / stroke
• current smoking / obesity
• uncontrolled blood pressure / LDL / T2DM

Unmet Need

Over the last 50 years, incidence has declined 67%, but treatments with a direct mode of action are still urgently needed.

High risk Target populations

Risk population / outcome
• recent stroke (14% of 700,000 within one year)
• include MI into outcome to increase power.

ASDERA – Overview

Derisking

How: Finding targeted therapies from genetics through a computational biostatistics platform,

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

1800 Gauss-Legendre

1900 Ohdner

9 Byte ANOVA

1965 IBM 256 kB PCA

1985 PC 16 MB Bayes

1948 Hoeffding

2001 GPU 4 GB u-Stat
ASDERA’s Novel Discovery Technology and α-cyclodextrin Hit

### Discovery Platform
- Analyzed 3 independent BC populations
- Results suggested a novel treatment concept

### Genetic results
- Consistent results showed metastases are associated with:
  - variations along the endo-/exocytosis (EEC) pathway
  - variations in the PI cycle, which regulates EEC
- Considerable overlap with genetic risk factors of AD and PD.

### Independent Confirmation
- Of the 27 EEC genes identified, 24 have known function in BC.
  - “Derailed endocytosis”\(^{[Mosesson 2008]}\) is a known component of BC etiology.
  - “Deranged endocytosis”\(^{[vanDooren 2014]}\) is also a known component of AD.

### Mode of Action
- ASD-003..006 is an innovative (optionally oral) derivatives of αCD; they down-regulate endocytosis by scavenging serum phospholipids.
- βCD was effective in models of BC, AD, PD, CAD, ...

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**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, incl. **PRKCCQ**

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

**Endo-/Exocytosis (EEC)**

![Genes Table](Image)

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Branches of Endocytosis

Late endosome and multivesicular body

PI(3,5)P

PAS complex: PIKFYVE/VAC14/FIG4
SNX5

Lysosome

GLB1
SCARB2
(LIMP-2)

RAB7
CHMP4
SYT1
UNC13C
RAB32
SNARE complex

VAMP7
SNAP25
STX7/8

RAB27
STXBP1
(VPS16-A18-HOPS complex)
ANXA4

SNARE complex

VAMP7
SNAP23
STX4
STXBP4

Ca2+
TRPM2
MTMR1
PI(5)P
PI4K

PI(4,5)P

RAB25
RAB11FIP1
RAB11

RAB9
Recycling endosome

Recycling endosome

Synto-17

Trans-Golgi network

β1 Integrin

active

STX6/VAMP3 complex


LRRK2
PSEN1/2

LDL

LY

β1 Integrin

LDL

AP2

Clathrin

Lysosome

Foam Cell

Plaque

Macrophage

Cancer

AD/PD

Atherosclerosis

Lysosomal Dysfunction in ....

Cancer

AD/PD

Atherosclerosis

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... can be Compensated by Down-Regulating the PI Cycle

Colored arrows sequence of PIPs involved in EEC.

Pink genes associated with BC in genetic analysis.

**Hypothesis:**
Scavenging serum phospholipids "re-rails" endocytosis

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**Cyclodextrins scavenge Lipids**

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

βCD also scavenges Cholesterol

Permanent Hearing Loss

αCD<sub>n=6</sub> / βCD<sub>n=7</sub>

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ASD-003 (HPαCD*) is >2× as effective as HPβCD against migration

MCF-7 human ER⁺ BC cells
ASD-003
HPβCD

MDA-MB-231 human ER⁻ BC cells
ASD-003
HPβCD

ANOVA: p = .0252

αCD is more effective than HPβCD in Lysosomal Storage Diseases
ASDERA – Successful test of bCD in many disease models

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ASDERA – Successful test of bCD in many disease models

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ASDERA – IP and Market

**IP Protection**
- US/EU patent for αCD derivatives, expiration 2039

**Market Size**
- BC: R+BC: 250,000 × 10 yr × 10% × $20,000/yr = $5.0 B of $50.0 B
- TNBC: 37,000 × 4 yr × 50% × $20,000/yr = $1.5 B of $3.0 B
- ND: AD: 5,500,000 × 10% × $20,000/yr = $11.0 B of $110.0 B
- PD: 1,000,000 × 10% × $20,000/yr = $2.0 B of $20.0 B
- CAD (prev): 100,000,000 × 10% × $1,000/yr = $10.0 B of $100.0 B

**Time to Market**
- 0.5 yr (prevention of CAD), 3 yr (GBA-PD), 5 yr (TNBC)

**Partnering Options**
- Investment
- Licensing/Joint Development Partnership with options for consideration:
  - Milestones
  - Royalty
  - Right-to-acquire option
  - Regional or global commercialization rights

ASDERA – Summary

**ASD-003/4/5**
- Proposed first drug to target metastases in BC, progression in AD/PD
- Proposed first drug to prevent the BC/AD/PD/CAD (“baby αCD”).

**Unmet Need**
- 30% of women diagnosed with early-stage BC will develop metastases.
- No treatment to prevent metastases in BC and other carcinomas
- No treatment for TNBC, except radiation and chemotherapy
- No treatment for AD and PD
- No prevention for BC (metastases), AD, and PD; limited success in CAD

**Product**
- Market-exclusive derivatives of α-cyclodextrin (aCD), pat. pending

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

**PoC**
- βCD was effective in animal models, but may cause hearing loss
- αCD is 2× as effective against endocytosis (β1 integrin), without ototoxicity

**IP Market**
- Patent filed in US, EU, ...
- Total US market (at 10% market penetration) ~$30B/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.

### Result

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

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

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