Reducing the side effects of chemotherapy through targeted drug delivery to solid tumors

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The Cytosolix Team

Management Team

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Lead Inventor, Associate Research Scientist,
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Wayne D. Klohs, Ph.D.
Oncology Drug Development Strategy Advisor
Formerly Senior VP of Global Oncology, Astellas Pharma
Formerly CEO, Pi Squared Therapeutics

Terrence W. Doyle, Ph.D.
Drug Discovery and Development Advisor
Formerly Director of Preclinical Cancer Research, BMS
Formerly CSO, Vion Pharmaceuticals

J. Paul Eder, M.D.
Clinical Advisor
Director, Phase I Program at Yale Cancer Center
Formerly Medical Science Director, AstraZeneca

Stephen B. Sasson Ph.D.
Regulatory Strategy Advisor
Formerly VP of World Regulatory Affairs, and
Clinical & Medical Sciences Team Leader, Pfizer

Advisory Team

Currently Recruiting
Management Team Candidates

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Clinical & Medical Sciences Team Leader, Pfizer
Problem:

Chemotherapy is essential, but side effects limit effectiveness.

Current Solutions:

Tumor-targeted drug delivery such as ADCs improve outcomes. Useful molecular biomarkers are rare, and fail to reach >90% of patients.

Our Solution:

Target drug delivery to a physiological biomarker of solid tumors: Acidity. Enables targeting of ~95% of cancers.
A Universal Biomarker of Solid Tumors

- Tumor acidity is an unavoidable consequence of cancer metabolism
- Recognized for ~100 years, but greatly underestimated
  - Classic tools underestimated acidity due to blood dilution as pH ~6.8
- New molecular pH-probes show tumor acidity is far stronger
  - The tumor cell surface is pH ~6.2
- New diagnostics targeting tumor acidity validate this biomarker in man:

Human Bladder Cancer

![White Light](Image1)
![Acid-Targeted Fluor](Image2)

Golijanin, et al. PNAS 2016. 113,42. 11829.
How we target drugs via tumor acidity

Tissue pH affects the membrane permeability of weakly-ionic drugs
Basic drugs – a problem in oncology

Problem:
Weak-bases are poorly-suited for solid tumors
- >25% of approved oncology drugs
- >50% of modern classes, e.g. kinase inhibitors

Very few weak acids with $pK_A$ targeting tumor pH

**Tumor Activated Permeability (TAP) Therapy**

**Strategy A: Weakly-acidic prodrugs**

Applications: Anthracyclines, Alkylators, Antimetabolites
Re-Engineering Modern Inhibitors

Strategy B: Re-engineer weak base drugs into weak acids

Applications: Kinase Inhibitors, PARP inhibitors, SERMs
TAP-Doxorubicin Prodrug Profile

Advantages: Potentially curative & widely effective

Problem: All anthracyclines are bases

Key side-effect: Cardiotoxicity

Indications:

1. Soft Tissue Sarcoma
   - Orphan indication
   - Unmet need, Doxorubicin approved
   - >20% of pediatric cancers – Cardiotox is a major concern

2. Triple-Negative Breast Cancer
   - Doxorubicin approved and effective
   - Cardiotox limits adjuvant use

3. Numerous Combinations
TAP-ProDox Achieves pH-Targeted Activity

TAPs impart ~100-fold improvement over doxorubicin through tumor-selective uptake:

**Doxorubicin**

**ProDox-YU241531**

**ProDox-YU252348**

**ProDox-YU244206**

**Dox-Prodrug**

YU241531 (June 2017)

YU252348 (July 2017)

YU244206 (June 2017)

pH 6.2 IC₅₀ = 21.5 µM

pH 7.4 IC₅₀ = >100 µM

pKₐ = 8.3 (basic)

pKₐ = 4.61 (acidic)

pKₐ = 6.05 (acidic)

pKₐ = 5.94 (acidic)

15.5x

12.1x

7.6x

7.2x

Detrimental IC₅₀ Bias

Tumor-Targeting

Tumor-Targeting

Tumor-Targeting

CONFIDENTIAL – Do Not Distribute
Efficacy without toxicity

Tumor Growth Delay

Side Effects

QDx5 IV efficacy in 10 week Balb/c with flank EMT-6 mammary carcinoma:
The Cytosolix Platform

- Impart benefits of tumor targeting to most drugs
- Established, low-risk path to clinic
- Market Expansion Strategy:
  - Initial Target Markets
    - Precision Indication (e.g. BRCAm Ovarian)
  - First Expansion
    - Class-Established Indications and Combinations
  - Second Expansion
    - All Solid Tumor Indications
    - Newly Enabled Combinations

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Market Landscape

Market Opportunity for a Universal Biomarker of Solid Tumors:
- Addresses ~95% of cancers
- First-in-class and first targeted options for areas of unmet need

Competitive Advantages of Our Technology:

<table>
<thead>
<tr>
<th></th>
<th>Dev. Cost</th>
<th>Dev. Time</th>
<th>Target Breadth</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAP Platform</td>
<td>Low</td>
<td>Fast</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Antibody-Drug Conjugates</td>
<td>High</td>
<td>Slow</td>
<td>Poor</td>
<td>Good</td>
</tr>
<tr>
<td>Receptor-targeted Prodrugs</td>
<td>Low</td>
<td>Fast</td>
<td>Poor</td>
<td>Moderate</td>
</tr>
<tr>
<td>Nanoparticle EPR</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Good</td>
<td>Poor</td>
</tr>
</tbody>
</table>
Intellectual Property Position

- Patent-pending platform IP
- Patent-pending novel targeted warheads
- All unpublished pending commercialization

Our platform IP casts a wide net, protecting our library of novel acids tuned to discriminate between healthy and tumor pH, via their pKₐ.

- Evaluated >60 model TAP compounds
- Validated 6 novel classes of tunable weak acids
R & D Pipeline

**Chemistry**
- **In Vitro Activity Assays**
- **In Vitro ADME**
- **In Vivo MTD/PK**
- **In Vivo Efficacy**

**PARP Program**
- (3 leads)

**DNA-Alkylator Program**
- (6 leads)

**Anthracycline Program**
- (3 leads)

**Lead Candidate Elections**

**Candidate Elections**
- Pre-IND Meeting
- IND
- EoP1 Meeting

**Discovery**
- (4-6 months)
- Series A – Tranche 1

**Development**
- (12-18 months)
- Tranche 2

**Phase I**
- (~12 months)

**Phase II/III**
- (~12 months)
- Series B

= Series A Milestone
Value Creation Strategy

• Broad and efficient discovery efforts
  – Developing multiple preclinical assets to Lead Candidate Election
  – Co-development partnerships or outlicensing

• Focused clinical development strategy
  – Unmet need and orphan indications for rapid regulatory
  – Indications with short primary endpoints
  – Precision medicine indications – biomarker defined patient population

• Initial clinical validation of the platform will inflect value of all preclinical assets

Over $1.3M in grants and non-dilutive seed funding since 2015
have built Cytosolix into an investment-ready oncology platform
Blavatnik study plan:

Target 1 - Re-engineered TKI

3rd Gen EGFR inhibitor - Osimertinib
- EGFR(T790M) NSCLC
- Blockbuster LOE opportunity in 2022

<table>
<thead>
<tr>
<th>Study</th>
<th>Cost</th>
<th>Duration</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK/PD Bioavailability</td>
<td>$30K</td>
<td>4 Weeks</td>
<td>Initial Dose</td>
</tr>
<tr>
<td>Single-Dose PD</td>
<td>$59K</td>
<td>6 Weeks</td>
<td>Continuous Dosing Schedule</td>
</tr>
<tr>
<td>Continuous-Dose Efficacy</td>
<td>$75K</td>
<td>8 Weeks</td>
<td>Head-to-Head Efficacy</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$164K</strong></td>
<td><strong>18 Weeks</strong></td>
<td></td>
</tr>
</tbody>
</table>
Blavatnik study plan:

**Target 2 - Targeted DNA-crosslinker prodrug**

- Potentially curative, Linear dose response
- Dose limited by myelosuppression
- Target indication: BRCA-deficient ovarian cancer
  - Unmet need, orphan indication
  - Established sensitivity to DNA-crosslinkers
  - ~15% of Ovarian - Incidence ~20K

<table>
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<th>Study</th>
<th>Cost</th>
<th>Duration</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK/MTD</td>
<td>$41K</td>
<td>4 Weeks</td>
<td>Initial Dose</td>
</tr>
<tr>
<td>Efficacy</td>
<td>$22K</td>
<td>7 Weeks</td>
<td>Head-to-Head Efficacy</td>
</tr>
<tr>
<td>Toxicity</td>
<td>$36K</td>
<td>5 Weeks</td>
<td>Myelosuppression Nadir</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$99K</strong></td>
<td>16 Weeks</td>
<td></td>
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</tbody>
</table>
• Platform targets drug delivery to 95% of cancers
• 100-fold better tumor selective activity
• Improves TI and overcomes dose-limiting toxicities
• Patent-pending composition and method IP

<table>
<thead>
<tr>
<th>Study</th>
<th>Cost</th>
<th>Duration</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMPK/ADME</td>
<td>$31K</td>
<td>4 Weeks</td>
<td>De-risk in vitro tox</td>
</tr>
<tr>
<td>Kinase Inhibitor POC</td>
<td>$164K</td>
<td>18 Weeks</td>
<td>Oral strategy preclinical POC</td>
</tr>
<tr>
<td>DNA-crosslinker POC</td>
<td>$99K</td>
<td>16 Weeks</td>
<td>Prodrug strategy preclinical POC</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$294K</strong></td>
<td><strong>22 Weeks</strong></td>
<td><strong>De-risking and 2x Lead Assets</strong></td>
</tr>
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Re-Engineering Modern Inhibitors

Reforming modern drug design for the solid tumor microenvironment
Re-engineering weak base drugs

Afatinib
NSCLC EGFR(ex19del,L858R)
Side effects:
~90% rash and diarrhea

Osimertinib
NSCLC EGFR(T790M)
Side effects:
~60% lymphopenia
~40% rash and diarrhea
Kinase Targets

1. **EGFR inhibitors (Osimertinib)**
   - EGFR(T790M) NSCLC
   - Blockbuster LOE opportunity in 2022

2. **HER2/ERBB2 inhibitors (Neratinib)**
   - Adjuvant in HER2+ Breast Cancer
   - Reducing cardiotoxicity and diarrhea could move this to a 1\textsuperscript{st} line option

3. **CDK4/6 inhibitors (Palbociclib)**
   - ER+, HER2- Breast Cancer (combination with antiestrogen treatment)

4. **ALK inhibitors (Crizotinib)**
   - ALK+ and ROS-1+ NSCLC
Novel Targeted DNA-Crosslinkers

**Advantages:** Potentially curative due to linear dose-response

**Problem:** Constitutively active in blood

**Key side-effect:** Myelosuppression

**Pharmacology:** Administration – IV

**Precision Indications:**

1) **BRCA-mutant ovarian cancers**
   - Unmet need, orphan indication
   - Established sensitivity to DNA-crosslinkers
   - ~ 15% of Ovarian is BRCAm - Incidence ~22K

2) **All solid tumors w/ somatic HR defect**
   - Includes BRCA-related and FA-related genes (~25-50%)
   - Leverage biomarker development partnership (Sema4)
   - Precision opportunity, tumor genotype-defined indication
Tumor acidity influences the efficacy of weakly ionic drugs:

Our proof-of-concept TAP Prodrugs of Doxorubicin are stable in serum, and release Doxorubicin in cytosol.

**Serum Bioavailability**
- 

<table>
<thead>
<tr>
<th>Compound</th>
<th>Serum Availability</th>
</tr>
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<tbody>
<tr>
<td>YU241526</td>
<td>~4 to 8 hours</td>
</tr>
<tr>
<td>YU241527</td>
<td></td>
</tr>
<tr>
<td>YU241528</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td></td>
</tr>
</tbody>
</table>

**Cytosolic Disulfide Reduction**
- 

<table>
<thead>
<tr>
<th>Compound</th>
<th>Disulfide Cleavage</th>
</tr>
</thead>
<tbody>
<tr>
<td>YU241527</td>
<td>~2 to 6 minutes</td>
</tr>
<tr>
<td>YU241528</td>
<td></td>
</tr>
</tbody>
</table>

**Linker Cleavage and Drug Release**
- 

<table>
<thead>
<tr>
<th>Compound</th>
<th>Doxorubicin Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>YU241526</td>
<td>~120 minutes</td>
</tr>
<tr>
<td>YU241527</td>
<td></td>
</tr>
<tr>
<td>YU241528</td>
<td></td>
</tr>
</tbody>
</table>
Tumor Acidity is a Clinical Biomarker

Heterogeneous acidity differs moderately with depth in solid tumors

Small metastases are highly acidic at their rapidly dividing surface:

Large solid tumors also have high acidity in and around necrotic cores:

Since greater acidity correlates with metastasis and invasiveness, TAP Prodrugs should be most effective against metastatic disease, where therapy is most needed.
Pharmacokinetics

The acidic TAP-Doxorubicin Prodrug, YU241528, shows a pharmacokinetic profile typical of an acidic drug, contrasting greatly from the basic pharmacokinetics of doxorubicin, following i.v. injection in adult Balb/c mice. The TAP platform thus plays a dominant role in controlling drug distribution in vivo.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Units</th>
<th>Doxorubicin</th>
<th>YU241528</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC to tlast</td>
<td>ug.h/L</td>
<td>1898</td>
<td>29,767</td>
</tr>
<tr>
<td>AUC to infinity</td>
<td>ug.h/L</td>
<td>2165</td>
<td>29,767</td>
</tr>
<tr>
<td>AUMC to infinity</td>
<td>ug.h/L</td>
<td>52159</td>
<td>41,356</td>
</tr>
<tr>
<td>Mean residence time</td>
<td>h</td>
<td>24.1</td>
<td>1.39</td>
</tr>
<tr>
<td>half-life</td>
<td>h</td>
<td>16.7</td>
<td>0.96</td>
</tr>
<tr>
<td>Clearance</td>
<td>L*h/kg</td>
<td>1.9</td>
<td>0.67</td>
</tr>
<tr>
<td>VD steady state</td>
<td>L/kg</td>
<td>44.5</td>
<td>0.93</td>
</tr>
<tr>
<td>C0</td>
<td>ug/L</td>
<td>394</td>
<td>48,777</td>
</tr>
<tr>
<td>Cmax</td>
<td>ug/L</td>
<td>266</td>
<td>37,811</td>
</tr>
<tr>
<td>Dose</td>
<td>ug/kg</td>
<td>4000</td>
<td>20,000</td>
</tr>
<tr>
<td>MW</td>
<td>g/mol</td>
<td>543</td>
<td>813.84</td>
</tr>
</tbody>
</table>

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