Product Development-Focused Translational Research

A Collaboration Model to Bring New Treatments to Bladder Cancer Patients

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Houston, TX
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Vision, Mission & Core Hypothesis

- Change the standard of care for patients across the life span suffering from cancer and rare diseases
- Discover and develop drugs, diagnostics and medical devices with clear paths to market
- Investment in high potential academic projects with industry-experienced input and leadership will enhance the yield of commercial products that benefit patients
Factors Contributing to the “Valley of Death”

- Project Selection
- Funding
- Expertise
- IP Management
- Institutional Commitment
- Investment vs. Grant
- Fragmented R&D
Implementing the Best Aspects of Successful Disease Philanthropy Models

- Basic Research
- Direct Investment to Enable Translation
- For-Profit Partner

Discoveries → Products

Logos: accelerate brain cancer cure, THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH, MMRF Multiple Myeloma Research Foundation, LEUKEMIA & LYMPHOMA SOCIETY, BILL & MELINDA GATES FOUNDATION, Cystic Fibrosis Foundation, CHDI FOUNDATION.
Investment Thesis

- Unmet Medical Need
- Scientific Solution
- Project Narrative, History and Investment Request
- Data Summary
- Path to Market
- Market
- Intellectual Property
- Team and Advisors
Industry Input into Project Selection

Steve Averbuch, MD
VP, Translational Clinical Development & Pharmacodiagnostics
Bristol-Myers Squibb
Princeton, NJ

John Fisher, MD
Founder, Biopsy Sciences and Interventional Radiologist
Tampa, FL

Lili Portilla, MPA
Director of Strategic Alliances
NCATS at NIH
Rockville, MD

Mike Webb, MBA
IAMI Advisory Board Chair
CEO, Tyrogenex, Xcovery
Boston, MA

Tom Wiggans, RPh, MBA
Founder and CEO
Dermira
Menlo Park, CA
De-Risking Projects

- Multidisciplinary, multi-organizational teams co-led by faculty inventor and industry-experienced project manager
- Milestone-based investments not grants
- Invest to value inflection point, $200K-$800K
- Work performed by
  - Faculty
  - University R&D infrastructure
  - Collaborators
  - Contract research organizations
- Operating MOU with Tech Transfer
  - Patenting strategy
  - Marketing strategy
  - License negotiation
Partnering to Bring New Treatments to Patients

**DISCOVERY**
- CB-5083 - Multiple Myeloma
- CB-5083 - Advanced Solid Tumors
- LOW DOSE DAUNORUBICIN - AML, B-ALL, T-ALL
- MSCTC-0010 - Graft vs Host Disease
- CICLOPIROX PRODRUG - Bladder Cancer
- NANOTAX® - Peritoneal Cancers

**DEVELOPMENT**
- CAR T-CELL - Adult DLBCL
- CAR T-CELL - Neuroblastoma
- CICLOPIROX OLAMINE - AML
- CAR T-CELL - Pediatric ALL
- CAR T-CELL - Melanoma
- PYRIMETHAMINE - MDS

**EXPERIMENTAL THERAPEUTICS**
- ETHACRYNIC ACID - Bladder Cancer
- MELPHALAN-CAPTISOL® - Myeloablation
- AURANOFIN (RIDAURA®) - CLL
- NIACINAMIDE - PKD
- NICOTINAMIDE - PKD
- TIGECYCLINE - AML
Nine Products Licensed, One Marketed Product
Ciclopirox Olamine – Antifungal Agent

- Olamine salt form of ciclopirox (CPX-O) created by innovator firm to enable topical formulation development as an antifungal agent.
- Ciclopirox chelates multivalent metals including aluminum and iron, resulting in inhibition of metal dependent enzymes responsible for degradation of peroxidases within the fungal cell\(^1\).
- Not enough systemic absorption following topical administration to achieve adequate drug exposure.
- Olamine salt has poor water solubility.

\(^1\) Loprox® Drug Monograph
Rediscovery of Ciclopirox

LLS-sponsored investigator identified ciclopirox (CPX) as the top candidate in a survivin promoter activation screen of 4,800 off-patent drugs and natural products for potential anti-cancer activity¹

- Also cytotoxic to leukemia stem cells
- Cancer specificity
- In vivo xenograft proof of principle established following oral dosing
- LLS subsequently made a product development investment in CPX for AML

¹ Eberhard et al, Blood 2009 114(14):3064-73
Oral Ciclopirox in Refractory Hematologic Malignancies

Phase I safety, dose tolerance, PK/PD trial in patients with hematologic malignancies

- CPX-O administered as oral suspension
- Biological activity (survivin) observed at doses > 10 mg/m²
- No clinical responses but hematologic improvement in two patients
- Absorption complete but low circulating concentrations of CPX suggested extensive first pass effect
- Dose-limiting GI toxicity associated with oral QID dosing

Ciclopirox Prodrug for the Treatment of Bladder Cancer

- Rapid and complete metabolism
- Composition of matter patents issued
- Three-step synthesis process
- Outstanding water solubility
- Injectable formulation

- Active metabolite
- 32 publications describing anticancer activity in 17 different cancers
- Rapid and complete renal elimination\(^1\)
- Reactivation of CPX following hydrolysis of glucuronide metabolite in urine

\(^1\) Kellner et al, Arzeim-Forsch 31:1337-1353, 1981
**In Vitro Proof of Principle**

**CPX Inhibits Bladder Cancer Cell Proliferation**
- IC50 (48 h): 4 μM
- IC50 (72 h): 1.5 μM

**CPX Inhibits 2D Colony Formation**
- 0.5 μM
- 1.0 μM
- 5.0 μM

**CPX Inhibits Spheroid Formation**

**CPX Arrests Cells at the S Phase of the Cell Cycle**

**CPX Induces Apoptosis**
- PI
- Annexin V (FITC)
- Merged
Novel Mechanism of Action

CPX Effects on Notch Pathway Genes

CPX Inhibits the Y-Secretase Protein Complex via Removal of Presenilin-1

Inhibition of the Y-Secretase Protein Complex Results in Decreased Downstream Target Proteins

CPX Inhibits Notch-1, -2 and -3 Isoforms

Overexpression of NICD Decreases CPX Antiproliferation Effect
CPX-POM Decreases Tumor Size and Stage at MTD* and ½ MTD

Significantly¹ Lower Bladder Weights in CPX-POM Treated Animals

Migration to Lower Stage Tumors in CPX-POM Treated Animals

Bladder tissue histochemistry demonstrates inhibition of Notch signaling

¹ 100 mg/kg p = 0.013; 200 mg/kg p = 0.036

* MTD = 200 mg/kg IP
Influence of CPX-POM Dose and Dose Frequency* on Tumor Size and Stage

Significantly¹ Lower Bladder Weights in CPX-POM Treated Animals

Migration² to Lower Stage Tumors in CPX-POM Treated Animals

* 100 mg/kg QD versus AD (three times weekly dosing)

¹ 25 mg/kg QD p = 0.006; 50 mg/kg QD p = 0.024; 100 mg/kg QD p = 0.008; 100 mg/kg AD p = 0.001

² Statistically significant (p = 0.039) migration toward lower stages in the treatment group; Pearson’s correlation coefficient (R = 21.6) suggests weak association between dose and tumor stage
Rate and Extent of Renal Elimination Results in Urine CPX Concentrations That Exceed In Vitro IC50 by 15-30x

- Inactive CPX-POM rapidly and completely metabolized to active CPX in plasma
- Excellent CPX bioavailability demonstrated in mice, rats and dogs following IV and SQ CPX-POM
- Entire dose rapidly and completely eliminated in urine
- Four percent of dose excreted as CPX
- Inactive glucuronide metabolite (76% of dose) is hydrolyzed in urine of bladder cancer patients to reactivate CPX

*IC50 = 2-4 μM
Proving the Core Hypothesis

✓ WW composition of matter patents
✓ Drug synthesis process ready for transfer
✓ Injectable formulation
✓ In vitro proof of principle in NMIBC and MIBC
✓ In vivo proof of principle in BBN mouse model
✓ Pharmacokinetic proof of principle
Traditional Paths to Product Development

Traditional Licensing Deal

KU Invented P97 Inhibitors

CB-5083

NCI NExT Program

Metarrestin

Submit a NExT Application

Phase I Multiple Myeloma Trial
Phase I Advanced Solid Tumors Trial

Faculty Startup

Novel Polysaccharide Chemically Linked with Cytotoxic Agents to Deliver Drug to Lymphatics

KUCC Pilot Award

R01 CA173292

Hylapharm Inc.

NCI Contract HHSN261201500047C
Innovative Path to Commercialization

BioNovus Innovations LLC

- Formed by Kansas City investors and community leaders
  - Support IAMi vision and mission
  - Bring medical innovations to our patients
  - Grow regional biotech community
- Co-invest to “de-risk” projects, in return, first rights to negotiate license
- Commercialization
  - Development → Registration → Launch
  - Develop to Partner
- Project teams actively engaged in development
- Ciclopirox Prodrug first license executed under preferred partnership agreement
## 505(b)1 Development Path

<table>
<thead>
<tr>
<th>IND-Enabling Activities</th>
<th>Expected Timing</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type B Pre-IND Meeting with FDA</td>
<td>2Q 2017</td>
<td>✔</td>
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<tr>
<td>Injectable Formulation Development &amp; Transfer to a GMP Qualified Manufacturing Facility</td>
<td>4Q 2016 – 1Q 2017</td>
<td>✔</td>
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<tr>
<td>Bioanalytical Methods Transfer, Development &amp; GLP Validation</td>
<td>2Q 2017</td>
<td>✔</td>
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<tr>
<td>API Scale-up</td>
<td>3Q 2016</td>
<td>✔</td>
</tr>
<tr>
<td>Manufacture GLP Toxicology Supplies and Stability</td>
<td>3Q 2016</td>
<td>✔</td>
</tr>
<tr>
<td>GMP Drug Substance Manufacture, Release &amp; Stability</td>
<td>4Q 2016 – 1Q 2017</td>
<td>✔</td>
</tr>
<tr>
<td>GLP 28-Day Rat Toxicology</td>
<td>4Q 2016</td>
<td>✔</td>
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<tr>
<td>GLP 28-Day Dog Toxicology</td>
<td>4Q - 2016</td>
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<tr>
<td>GLP Safety Pharmacology</td>
<td>1Q - 2Q 2017</td>
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<tr>
<td>Mutagenicity</td>
<td>-</td>
<td>✔</td>
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<tr>
<td>Manufacture GMP Clinical Supplies</td>
<td>1Q -2017</td>
<td>✔</td>
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<tr>
<td>IND Preparation and Submission</td>
<td>3Q 2017</td>
<td>✔</td>
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<tr>
<td>FDA Review</td>
<td>3Q 2017</td>
<td>In Progress</td>
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<tr>
<td>Initiate Phase 1 Safety, Dose Tolerance, PK/PD study</td>
<td>4Q 2017</td>
<td>Planned</td>
</tr>
</tbody>
</table>
Drug Development Timeline

License Agreement

Confirmatory Proof of Principle Study in Validated Animal Model

Drug Manufacturing Initiated

Pre-IND Meeting with FDA

Clinical Advisory Meeting

Toxicology Studies Initiated

First Patient Enrolled

IND Submission to FDA

11/2015

8/2017
## It Takes a Village

### Inventors
- S. Anant
- M. Tanol
- S. Weir

### CicloMed LLC
- T. Ham, President & CEO
- B. McCulloch, CMO
- R. Wood, Project Mgmt
- S. Weir, CSO

### IP Management
- P. Slicer
- M. Koenig

### Drug Development
- M. Baltezor
- G. Reed
- S. Weir
- R. Wood
- W. McCulloch
- M. McKenna

### Cancer Biology
- S. Anant
- J. Taylor

### Clinical Advisory Board
- M. Cookson
- J. Holzbeierlein
- G. Steinberg
- J. Taylor
- W. McCulloch
Our Patients Are Waiting!

THE UNSPEAKABLE TRUTH

We have a type of cancer people think only affects old men. | More likely to come back after treatment than any other, it is the only top ten cancer where survival rates are getting worse. | The most expensive cancer to treat, it receives just 0.6% of research money. | Only half of us will survive it. | Why is no-one talking about it?

Don’t you think it’s time to make some noise?

www.shoutoutaboutbladdercancer.org