Public-Private Partnership to Bring New Treatments to Patients

Repurposing for Rare Diseases and Orphan Drug Development

6th Annual Drug Repositioning, Repurposing and Rescue Conference
Scott J. Weir, PharmD, PhD
Chicago, IL
28 June 2017
“Leverage unique regional scientific assets to build a nationally significant cancer research center that is a leading institution for transforming laboratory and bedside discoveries into new therapeutic approaches”
“few universities have established an overall strategy to foster innovation, commercialization and spillovers”

Kauffman Foundation 2007
Factors Contributing to the Valley of Death

- Project Selection
- Funding
- Expertise
- IP Management
- Institutional Commitment
- Investment vs. Grant
- Fragmented R&D
Vision and Mission

Vision

- Change the standard of care for pediatric, adolescent and adult patients suffering from cancer and rare diseases

Mission

- Discover and develop pharmaceuticals, diagnostics, and devices with a clear path to market

Core Hypothesis

- Investment thesis defined for high potential projects
- Industry-experienced input into project selection
- Invest to value inflection point
- Industry-experienced project management
Defining the Investment Thesis

- Unmet Medical Need
- Scientific Solution
- Project Narrative, History and Investment Request
- Data Summary
- Path to Market
- Market
- Intellectual Property
- Team and Advisors
Track Record to Date

**Develop**

- Medical Innovation Concept
- IAMl Investment Memo
- IAMl Product Development Focused Translational Research

**Demonstrate**

- BioNovus Partnership One Drug Product Licensed
- Existing Companies Two Drug Products Licensed
- Startup Companies Six Drug Products Licensed

**Disseminate**

- >200 Concepts
- 155 Investment Memos
- 48 Project Investments
- 9 License Agreements
- 1 Commercial Product
Traditional Paths to Enabling Product Development

Traditional Licensing Deal

KU Invented P97 Inhibitors

CB-5083

Phase I Multiple Myeloma Trial
Phase I Advanced Solid Tumors Trial

NCI NExT Program

Metarrestin

Submit a NExT Application

Faculty Startup

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

KUCC Pilot Award
R01 CA173292
Hylapharm Inc.
NCI Contract HHSN261201500047C
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
Repurposing a Topical Antifungal Agent

Extensive Ciclopirox Olamine Commercial Experience

- 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\(^1\)
- Patent expired, first marketed in 1982
- 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 as Top Candidate in 4,800 Drug Screen

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 activity

- Cytotoxic to leukemia stem cells
- Cancer specificity
  - Inhibits ribonucleotide reductase
  - Inhibits Wnt signaling
- In vivo xenograft proof of principle established following oral dosing
- LLS subsequently made a product development investment in CPX for AML

Eberhard et al, Blood 2009 114(14):3064-73
Phase I safety, dose tolerance, PK/PD trial in patients with hematologic malignancies

- CPX-O administered as oral suspension
- Biological activity 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

- Exclusivity established in US, Europe and Japan through composition of matter augmented by methods of use patents
- Optimized CPX-POM three-step chemical synthesis process
- In contrast to CPX-O, CPX-POM water solubility ~ 500 mg/mL enabled formulation of and administration by injection
- CPX-POM has minimal to no pharmacologic activity \textit{in vitro}
- Rapid and complete hydrolysis of CPX-POM to CPX demonstrated \textit{in vivo} in three species
- Selective delivery of CPX to the entire urinary tract

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{ciclopirox.png}
\caption{Ciclopirox Prodrug (CPX-POM)\hspace{1cm}Circulating phosphatases in blood \hspace{1cm} Activation of CPX\hspace{1cm} Ciclopirox (CPX)}
\end{figure}
Exploring Activity in Bladder Cancer

Phenotypic Drug Screen

- Complete recovery of oral C-14 dose in urine
- 87% within 6 hours
- >95% within 12 hours
- 4% CPX

CPX Elimination

- 79% inactive glucuronide conjugate
- β-glucuronidase activity in bladder cancer
6th most common cancer in men and women
- 79,030 new US cases in 2017
- 16,870 US deaths projected for 2017
- Overall 5-year relative survival is 78%

4th most common cancer site in men, projecting to remain so at least through 2024
- 608,620 patients living with bladder cancer¹
- 4:1 ratio men versus women
- Median age at diagnosis is 73 years
- Highest rate of recurrence among all known malignancies
- Most expensive malignancy to treat


- **Non-muscle invasive bladder cancer (NMIBC)**
  - 75% of new cases
  - Less aggressive but high recurrence and risk of progression to MIBC
  - Surgical resection and topical drug administration is standard of care

- **Muscle invasive bladder cancer (MIBC)**
  - 25% of new cases
  - High risk for metastasis
  - Radical cystectomy is standard of care but high morbidity and mortality risks limit procedure

- **Recurrence versus Progression**
  - Recurrence rate 31-78%
  - 25% of NMIBC progress to MIBC
  - Recurrence rate similar for low, medium and high grade disease
CPX Inhibits Bladder Cancer Cell Proliferation

IC50 (48 h): 4 uM
IC50 (72 h): 1.5 uM

CPX Inhibits 2D Colony Formation

CPX Inhibits Spheroid Formation

CPX Arrests Cells at the S Phase of the Cell Cycle

CPX Induces Apoptosis

In Vitro Proof of Principle
Novel Mechanism of Action

CPX Effects on Notch Pathway Genes

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

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

Overexpression of NICD Decreases CPX Antiproliferation Effect
In Vivo Proof of Principle

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

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

Bladder tissue histochemistry demonstrates inhibition of Notch signaling

* MTD = 200 mg/kg IP
In Vivo Proof of Principle

Influence of CPX-POM Dose and Dose Frequency*

Significantly\(^1\) Lower Bladder Weights in CPX-POM Treated Animals

* 100 mg/kg QD versus AD (three times weekly dosing)
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 \( p = 0.001 \)
Treatment of high risk NIMBC represents significant unmet medical need for approximately 12,500 patients annually
- Est. 7,500 newly diagnosed patients
- Est. 5,000 recurrent and progressing patients

High risk NMIBC patients defined as
- CIS
- Any Grade 3 (Ta or T1)
- Recurrent Ta Grade 1/Grade 2 tumors
- Multiple large (> 3 cm) Ta Grade 1/Grade 2 tumors
- Potential candidates for cystectomy

Of additional interest to urologists and medical oncologists
- Patients with upper urinary tract disease
- Poor candidates for cystectomy, e.g., patients > 80 years old
Activation of CPX in Blood

CPX-POM

CPX

Metabolism

Excretion

Site of Action

Selective Delivery to Entire Urinary Tract

*IC50 = 2-4 μM
## Results To Date

### Established In Vitro Proof of Principle in NMIBC and MIBC Cell Lines and Bladder Cancer Stem Cells

1. CPX inhibits cell proliferation, colony formation, bladdosphere formation and Notch signaling pathway proteins (Notch 1, 2, 3)
2. CPX arrests cells at the S-phase of cell cycle
3. CPX induces apoptosis

### Established Chemistry Proof of Principle

1. KU invention with US Composition of Matter and methods of use patents issued, composition of matter patents in Europe and Japan.
2. 3-step chemical synthesis process feasibility demonstrated for drug substance
3. Outstanding water solubility enabling formulation of and administration by injection
4. Prodrug has no activity in vitro
5. Rapid and complete hydrolysis in vivo of the prodrug to form ciclopirox

### Established Pharmacokinetic Proof of Principle in Mice, Rats & Dogs

1. PK of CPX-POM allows selective delivery of active CPX to the bladder and upper urinary tract (96% of dose)
2. CPX-POM rapidly disappears from plasma with near complete to complete formation of CPX
3. Urine CPX concentrations exceed in vitro IC50 by 10-20 fold at well tolerated doses
4. IV and SQ injectable routes of administration feasible

### Established In Vivo Preclinical Proof of Principle in a Mouse BBN Model

1. Treatment with once daily IP administration of CPX-POM 25 to 200 mg/kg for 4 weeks
2. Observed significantly lower bladder weights and lower tumor stage in CPX-POM treated mice
3. Evidence of decreased cell proliferation in bladder tumor tissue
4. CPX-POM inhibition of Notch downstream target proteins observed in bladder tumor tissue
5. CPX-POM was well tolerated with no pathologic evidence of urinary tract toxicity

## Partnered Data Package
<table>
<thead>
<tr>
<th>IND-Enabling Activities</th>
<th>Expected Timing</th>
<th>Status</th>
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<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>
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<tr>
<td>API Scale-up</td>
<td>3Q 2016</td>
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<tr>
<td>Manufacture GLP Toxicology Supplies and Stability</td>
<td>3Q 2016</td>
<td>✔</td>
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<tr>
<td>GMP Drug Substance Manufacture, Release &amp; Stability</td>
<td>4Q 2016 – 1Q 2017</td>
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<td>GLP 28-Day Rat Toxicology</td>
<td>4Q 2016</td>
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<td>GLP 28-Day Dog Toxicology</td>
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<tr>
<td>GLP Safety Pharmacology</td>
<td>1Q - 2Q 2017</td>
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<td>Mutagenicity</td>
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<tr>
<td>Manufacture GMP Clinical Supplies</td>
<td>1Q -2017</td>
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<tr>
<td>IND Preparation and Submission</td>
<td>3Q 2017</td>
<td>In progress</td>
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<tr>
<td>FDA Review</td>
<td>3Q 2017</td>
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<tr>
<td>Initiate Phase 1 Safety, Dose Tolerance, PK/PD study</td>
<td>3Q 2017</td>
<td>Planned</td>
</tr>
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Drug Development Timeline

- **License Agreement**: 11/2015
- **Confirmatory Proof of Principle Study in Validated Animal Model**: 5/2016
- **Drug Manufacturing Initiated**: 7/2016
- **First Patient Enrolled**: 7/2017

- **Clinical Advisory Meeting**
- **Toxicology Studies Initiated**
- **Pre-IND Meeting with FDA**
- **IND Submission to FDA**

**CicloMed**
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