Controlling cell death to protect human life

CBLB502 Medical and Curaxins Overview
Investor Day
June 8, 2011
This presentation includes forward-looking statements and predictions, including statements about potential revenue-bearing transactions, the market potential of CBLI’s technologies and product candidates, and the potential value of pipeline products. These statements represent the Company’s judgment as of the date of this presentation and are subject to risks and uncertainties that could cause actual results of events to differ materially from those expressed in such forward-looking statements. In particular, CBLI faces risks and uncertainties that it may not be able to sustain its business model, that revenues may be lower or expenses higher than projected, that product sales may not increase, that development of product candidates in the Company’s pipeline may not succeed or that commercial transactions may not go forward as planned.
Scientific and Clinical Program Goals

- Support Animal Rule-driven development of CBLB502 for biodefense applications
  - Mechanism of action studies: rational choice of biomarkers
  - Defining CBLB502 efficacy range
  - Determination and validation of human dose

- Moving CBLB502 to oncology clinic
  - Radiotherapy adjuvant (local irradiation models)
  - Chemotherapy adjuvant
  - Effect on tumors
CBLB502 in Preclinical Model of Local Irradiation

Goal:
- Justification of use of CBLB502 as a supporting care radioprotection adjuvant

Results:
- CBLB502 is efficacious against radiation-induced mucositis and dermatitis

Significance:
- Strong preclinical support of use of CBLB502 as radiotherapy adjuvant
- Justification of new application (protection from radiation-induced dermatitis)


Approval of “CBLB502 as supportive care” trial protocol in head and neck cancer patients by Scientific Review Committee of Roswell Park
Extending Indications of CBLB502
Mitigation of chemotherapy side effects and direct anticancer action

Irinotecan and CBLB502 against Wart colon tumors in Fisher rats

CBLB502 displays both supportive care and direct antitumor activities in rat model of colon cancer

CBLB502 rescues animals from Irinotecan toxicity with no interference with its antitumor activity

CBLB502 caused complete regression of tumors in part of the animals

CBLB502 displays both supportive care and direct antitumor activities in rat model of colon cancer
Radioprotective Effect of CBLB502 is Indirect

Granulocyte colony formation *in vitro* by mouse BM cells irradiated
Histological Atlas of CBLB502 Activity
Identification of Target Organs

Liver is the primary target organ of CBLB502
Assessing Role of Hepatocytes in Radioprotection: surgical exclusion of liver from blood circulation

Step 1. Occluding the hepatoduodenal ligament containing hepatic artery and portal vein with a non-traumatic clamp.

Step 2. CBLB502/PBS injections.

Step 3. The blood supply occluded for 30 minutes then clamp released and blood circulation restored.

Step 4. Mice were irradiated immediately after the surgery with 10 Gy TBI.

Step 5. Bone marrow cells isolated from femura and total colony formation estimated using MethoCult media and standard protocol for CFU assay.
No liver = No radioprotection of bone marrow

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Liver is the source of endogenous HP-protecting factors mobilized by CBLB502
TLR5 Activation Protects Liver from Fas

<table>
<thead>
<tr>
<th>H&amp;E</th>
<th>intact</th>
<th>anti-FAS</th>
<th>anti-FAS+CBLB502</th>
</tr>
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<tbody>
<tr>
<td>TUNEL</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>hemorrhagic lesions</td>
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</table>
TLR5 Agonist Protects Mice from Fas

**Mouse survival**

- PBS (n=16)
- CBLB502, 0.5 h (n=16)
- CBLB502, 2 hs (n=10)
- CBLB502, 6 hs (n=10)

**Liver condition**

**Caspase activation**

- Intact
- Fas
- CBLB502
- CBLB502 + Fas

**Liver enzymes**

- Serum ALT (U/L)
- Intact
- Fas
- CBLB502
- CBLB502 + Fas
**CBLB502 against liver metastases of colon cancer in mice**

- **CT26**, TLR5-negative syngeneic colon cancer, was grown as liver metastases in Balb/c mice

- Tumor growth was monitored using luminometer imager (tumors express luciferase)

- Tumor suppressive effect of CBLB502 is associated with tumor infiltration with immunocytes

![Image of tumor growth control and CBLB502 treatment](image)

**Graph**

- Intact, n=15
- CBLB502, n=19
- log rank p=0.0067
Direct Anti-tumor Effects of CBLB502

- Identification of target tissues enables rational choice of indications and regimens
- Phase I/II “CBLB502 as a single agent” trial protocol was approved by Scientific Review Committee of Roswell Park
CBLB502 as Direct Antitumor Agent

- Has direct suppressive effect in several animal models of TLR5-positive tumors (lung, colon cancer, melanoma)
- Effective against liver metastases regardless of TLR5 status of the tumor
- Acts by mobilizing antitumor immunity
- Expected to provide anti-tumor vaccination
- Fits several clinical trial scenarios, including liver metastasis of colon cancer, liver cancer, bladder cancer, H&N cancer, etc.
Prospective Clinical Trials of CBLB502 in Cancer Patients

- Reducing severity of mucositis and enhancing efficacy of radiotherapy of H&N cancer
- Reducing severity of bowel toxicity and enhancing efficacy of radiotherapy of pancreatic cancer
- Reducing severity of diarrhea in colon cancer patients treated with Irinotecan
- Treating primary hepatocellular carcinoma (liver cancer)
- Treating liver metastasis of colon cancer
- Treating liver metastasis of breast cancer
- Pre-operational treatment of prostate cancer

Many of these trials enable assessment of both supportive care and direct anti-tumor activity of CBLB502
CBLB502: Major Scientific and Clinical Updates

- Demonstration of CBLB502 efficacy in preclinical model of local irradiation
  - Approval of Phase I/II “CBLB502 as supportive care” trial in head and neck cancer patients by Scientific Review Committee of Roswell Park

- Discovery of direct anticancer action of CBLB502: from “supportive care only” drug to combined “supportive care and anticancer” drug
  - Approval of Phase I/II “CBLB502 as a single agent” trial by Scientific Review Committee of Roswell Park

- Demonstration of radiomitigating efficacy of CBLB502 against GI manifestation of acute radiation syndrome in primates that received extremely high radiation doses
  - Critical result for justifying extended indications of CBLB502

- Building of Histological Atlas of CBLB502 activity, identification of target organs
  - Path to optimal indications and regimens

- Completion of Phase Ib human dose validation trial
Curaxins
Anticancer drugs
Curaxin’s Targets p53, NF-κB, HSF1 in Cancer

Normal cell response to stresses

- Death or arrest
- Survival

CANCER

- Target for activation (doxorubicin, 5FU, cisplatin, etc.)
- Target for inhibition (bortezomib)
- Target for inhibition (geladanomycin)

infection

DNA damage

NFκB HSF1

p53
Curaxins Target FACT-dependent Transcription

NF-κB-dependent transcription requires FACT

Trap of FACT on chromatin blocks FACT-dependent transcription and causes CK2-mediated p53 activation

Gasparian et al., *Science Translational Research*, in final revision
Curaxin activator and inhibitor in live tumor cell:

- **p53** activator
- **NFκB** inhibitor
- **HSF1** inhibitor

Result in dead tumor cell:

- **p53**

Non-genotoxic anticancer drug candidates with triple mechanism of action suitable for use in combinations with conventional drugs.
## Curaxins: Safe Multi-targeted Drugs

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<tr>
<th>Property</th>
<th>Conventional drugs</th>
<th>Curaxins</th>
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<tbody>
<tr>
<td>Genotoxicity</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>NF-kB inhibition</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>p53 activation</td>
<td>yes</td>
<td>YES</td>
</tr>
<tr>
<td>Heat shock inhibition</td>
<td>no</td>
<td>yes</td>
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Curaxins in Cancer Prophylaxis

50% reduction in breast tumor incidence in transgenic MMTV-neu mice that were maintained on drinking water with non-toxic doses of curaxin CBLC137 during 10 months.

Lack of genotoxicity, combined with p53 activation and NF-κB and HSF1 suppression, opens the opportunity of using Curaxins as cancer preventing agents.
Curaxins

- Synthetic small molecules with proprietary structure
- Unique mechanism of action: simultaneously affect multiple molecular targets in cancer cell
- Efficacious in a broad spectrum of preclinical tumor models
- Mechanism of action enables additional clinical indications beyond cancer treatment (anti-inflammatory, anti-infective)
- First generation Curaxin CBLC102 is in clinical trial in patients with liver metastases
- New generation Curaxin CBLC137 is at advanced stage of preclinical development
Incuron – JV for Curaxin Development

- 50/50 joint venture with Bioprocess Ventures, Moscow

- ~$18M to reach Phase II for new generation of Curaxins in US and Russia and conduct human trials in liver cancer in Russia for CBLC102

- CBLI oversees mechanistic studies and formal development

- Phase Ib trial for CBLC102 in liver started October 2010

- IND-enabling studies for new generation of Curaxins on track for IND

- Demonstrates feasibility of model combining advantages of US and Russian development platforms
Milestones

- Start of pivotal animal efficacy studies for CBLB502 defense
- Start of definitive safety/dose validation trial in healthy volunteers for CBLB502 defense
- Start of CBLB502 Phase I/II trial in head and neck cancer patients for supportive care indication
- Start of CBLB502 Phase I/II trial in advanced liver metastases patients for safety/antitumor effect
- Completion of CBLC102 trial in liver cancer patients in Russia
- Filing of IND for studies of new generation curaxins
- Top level peer reviewed publications