Controlling cell death to protect human life

CBLB502 Defense Program Update
Investor Day
June 9, 2010
This presentation includes forward-looking statements and predictions, including statements about potential revenue-bearing transactions, the market potential of Cali'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.
CBLB502 as Medical Countermeasure (MCM) against ARS

Highly efficacious as a single dose
- Increases survival of irradiated primates from 20 to >70%
- Significantly reduces incapacitation of survivors
- Protects/treats both GI and HP components of acute radiation syndrome

Broad application time window
- From prior (24 hr) to & post (>48 hr) exposure to IR

Easy of use
- Single intramuscular injection suitable for self- or hospital administration

Established high-yield cGMP manufacturing process

Open IND for ARS indication

Safe
- Completed two Phase I safety trials in total of 150 healthy volunteers
Publications/Intellectual Property

- Published on April 11, 2008
- Validates scientific mechanisms of the drug and protective effect on mice & primates
- First publication on radioprotection in more than 30 years

- CBLI has exclusive rights to CBLB502 technology
- CBLB502 technology is subject of two patent families, which are actively being prosecuted by CBLI
- Patents granted in 11 countries including US
- European Patent Office has provided a notice of intent to grant
Animal Efficacy Rule – Path to FDA licensure

- Well understood mechanism of action (to provide biomarkers of efficacy)
- Compliance with CMC requirements
- Efficacy in two animal species including rhesus macaques using survival as endpoint
- Safety in healthy humans

Established FDA pathway to approve drugs where efficacy is unethical to test in humans
CBLB502 Mechanism of Action

CBLB502 $\rightarrow$ TLR5 $\rightarrow$ NF-κB

- IAPs, Bcl-2 $\rightarrow$ Suppress apoptosis
- SOD2, ferritin $\rightarrow$ Inactivate ROS
- Cytokines $\rightarrow$ Promote regeneration

RADIATION

Impaired immunity

Thrombocytopenia

Loss of GI integrity

Infections

ARS

Bleeding

DEATH

SURVIVAL

NIH Swiss mice, protection

Rhesus macaques

Vehicle (PBS), n=8

CBLB502 @ -45', n=11

CBLB502, 0.04 mg/kg (N=11) at -45'

CBLB502 @ +16h, n=12

CBLB502 @ +25h, n=10

CBLB502 @ +48h, n=12

Cytokines suppress apoptosis

IAPs, Bcl-2 inactivate ROS

SOD2, ferritin promote regeneration
Effect of CBLB502 on GI stem cell viability and stimulation

Crypt microcolony assay: BrdU incorporation 3d after 13Gy of TBI

Radiomitigation of GI component of ARS is funded by DoD
Effect of CBLB502 on HP stem cell viability and stimulation

Granulocyte colony formation *in vitro* by BM cells from irradiated mice

<table>
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<th>IR, Gy 502</th>
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<th>0</th>
<th>10</th>
<th>10</th>
<th>13</th>
<th>13</th>
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BM from Rhesus macaque 42 days post irradiation

control  CBLB502

CD2F1 mice, 9 Gy TBI, CBLB502 or vehicle (PBS) at +25 hours after TBI

Radiomitigation of HP component of ARS is funded by HHS/BARDA

Cleveland BioLabs, Inc
Liver (hepatocytes) is a major target of CBLB502 in vivo
• Differential gene expression reveals endogenous mediators of radioprotection
• Tissue atlas of CBLB502 effects indicates new potential indications

CBLB502 mobilizes multiple mechanisms of tissue protection that altogether mediate outstanding radioprotective and radiomitigating capacity of the drug

Deciphering these mechanisms facilitates drug applications

Mechanism ➔ Mediators ➔ Biomarkers ➔ New applications
Non-Clinical Safety

GLP Animal Safety Assessment

Completed:
- ✔ GLP mice acute and 2-week toxicology
- ✔ GLP NHP acute and 2-week toxicology
- ✔ GLP Seg II reproductive toxicology studies in rats and rabbits

GLP safety studies in two animal species confirmed low toxicity and lack of serious target organ effects

Remains to be completed:
- ✔ Seg I reproductive toxicology studies in rats (GLP)
- ✔ Seg III reproductive toxicology studies in rats (GLP)
Non-Clinical Efficacy
Animal Model Selection/Justification

- **Primary model: Rhesus macaques**
  Best-characterized primate ARS model, physiology similar to human, large animal

- **Secondary model #1: Mice**
  Best-characterized mammal ARS model but physiology is less close to human than primate

Backups (risk mitigation)

- **Secondary model #2: Cynomolgus monkeys**
  2nd best characterized primate ARS model, physiology similar to human, large animal

- **Secondary model #3: Dogs**
  Best characterized non-primate/non-rodent model of ARS, large animal
### Studies, Endpoints and Timeframe of Efficacy in NHPs

<table>
<thead>
<tr>
<th>TBI Dose</th>
<th>Parameter</th>
<th>Time relative to TBI (if applicable)</th>
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<tr>
<td></td>
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<td>-45'</td>
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<tr>
<td>LD&lt;sub&gt;50-70&lt;/sub&gt;</td>
<td>Survival benefit</td>
<td>+40%</td>
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<tr>
<td></td>
<td>Thrombocytopenia reduction</td>
<td>+++</td>
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<tr>
<td></td>
<td>Neutropenia reduction</td>
<td>+</td>
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<tr>
<td></td>
<td>Improved BM, spleen, thymus</td>
<td>+++</td>
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<tr>
<td></td>
<td>Improved GI mucosa</td>
<td>++</td>
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<td></td>
<td>Cytokine release (G-CSF, IL-6, etc.)</td>
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<td>Data on dose dependence of efficacy</td>
<td>TBD</td>
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<tr>
<td>LD&lt;sub&gt;10-20&lt;/sub&gt;</td>
<td>Thrombocytopenia reduction</td>
<td>+++</td>
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<td></td>
<td>Cytokine release (G-CSF, IL-6, etc.)</td>
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<tr>
<td></td>
<td>Data on dose dependence of efficacy</td>
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<tr>
<td>No TBI</td>
<td>Increased platelet levels</td>
<td>+++</td>
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<tr>
<td></td>
<td>Increased neutrophil levels</td>
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<td></td>
<td>Cytokine release (G-CSF, IL-6, etc.)</td>
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</tr>
<tr>
<td></td>
<td>Data on dose dependence of efficacy</td>
<td>√</td>
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+++: strong effect; ++: moderate effect; +: minor effect; √: data collected

**19 studies with total of 667 non-human primates**
• **Species:** rhesus monkey, *Macaca mulatta* (best-studied primate model in ARS); both sexes, young adults

• **Doses of radiation tested:** from ~LD10/40 to ~LD75/40 TBI

• **Efficacious times of treatment:** at least from -45’ to >48 hours *(treatment at 120 hours is not efficacious)*

• **Efficacious doses of CBLB502:** >=10 ug/kg is efficacious at all time points and radiation doses tested, 3 ug/kg was determined as EC50

**Summary of efficacy:** CBLB502 treatment increases survival (by up to 40-45%); reduces severity/duration of thrombocytopenia, reduces severity of neutropenia, reduces morphological damage in: BM, GI tract, spleen, thymus, LNs
Summary of CBLB502 Efficacy Features in Mouse Model

• **Species:** house mouse, *Mus musculus* (best-studied mammalian model in radiation-related studies); both sexes, young adults, multiple strains (ICR, NIH-Swiss, Balb/c, CD2F1, etc.)

• **Doses of radiation tested:** from ~LD30/30 to >LD95/30 TBI

• **Efficacious times of treatment:** efficacy from -24 to +25 hours relative to TBI

• **Efficacious doses of CBLB502:** >~20 ug/kg is efficacious at all time points and radiation doses tested, ~10 ug/kg was determined as EC50

**Summary of efficacy:**

increases survival; reduces morphological damage in BM and GI
Proposed NHP GLP Efficacy Study Setup(s)

- **Endpoints:**
  - Primary: Survival
  - Secondary: CBC, histology (BM, GI, lymphoid organs), biomarkers, PK

- **IR dose:** $LD_{50}-LD_{90}$ γ/X-ray-TBI (*TBD for supportive care*)

- **Duration of observation:** 60 days

- **CBLB502 doses:**
  - Vehicle (0 ug/kg)
  - Fully efficacious (beginning of plateau) CBLB502 dose

- **Time of injection:** +25 hours after TBI, [optional: +1 hour]

- **Supportive care:**
  a. Experiment I: None – symptomatic care only
  b. Experiment II: Prophylaxis with antibiotics, fluids/electrolytes
Institutions Performing Pivotal Efficacy Studies

- **Frontier Biosciences**
  - Extensive experience in primate IR studies
  - Large capacities
  - Previous relationship, ~20 studies successfully completed
  - GLP compliant, GLP/non-GLP studies successfully submitted to FDA

- **University of Illinois at Chicago Toxicology Research Laboratory**
  - Substantial experience in primate, mouse and dog IR studies
  - Medium capacities
  - Previous relationship, 4 completed and ongoing studies
  - GLP compliant, GLP/non-GLP studies successfully submitted to FDA

- **Pharmaron**
  - Significant experience in primate and dog IR studies
  - (Large) experimental capacities
  - Existing relationship, 1 ongoing study
  - GLP compliant, GLP/non-GLP studies successfully submitted to FDA
CBLB502
Bulk Drug Substance (BDS)
CBLB502 BDS and liquid drug product

- Re-engineered variant of FliC flagellin
- 329 amino acids
- Produced in *E. coli* as an intracellular soluble protein using expression plasmid
- High-yield cGMP mfg. process (*SynCo Bio Partners, Amsterdam, Netherlands*)
  - Several hundreds of thousands of doses (25-30g of BDS) per single manufacturing run
  - Three cGMP batches (July’07) (Feb’09) (Apr’10)
  - More than 50g of BDS is still available
  - *SynCo* was inspected by BARDA RQA Division in July 2009
- The cGMP drug product (*frozen liquid formulation in Phosphate Buffered Saline*) was used in Phase 1 clinical trials and all preclinical studies
  - 7,000 vials released in Aug’07 (4,500 vials are still available)
- The bulk drug substance and liquid drug product are stable for 24 months when stored at -20°C and -70°C (as of Oct’09)
CBLB502 Bulk Drug Substance

What’s Left?

• Small Scale Validation Work
• GMP validation of biopotency assay
• Three consistency batches at scale and large scale validation
• Compliance audit of all systems to ensure that SynCo is operating in full compliance with US FDA cGMP regulations and guidelines
• cGMP mfg. documentation for BLA filing
CBLB502
Final Drug Product (FDP)
CBLB502 Final Drug Product (FDP)

- Optimized Lyo DP formulation; single dose vial
  - CBLB502 + 10mM Histidine, 2% Glycine, 1% Trehalose, 0.01% Polysorbate 80 (Tween 80)
  - Stable for at least 12 months up to 40°C (as of Nov’2009)
  - Manufactured by Integrity Bio (Camarillo, CA)
  - ~4,000 vials per batch capacity

- Development and cGMP Batches
  **Non-GMP:** 100 ug and 2 mg per vial in Nov’08 and 30 ug/ml in June’09
  **cGMP:** 100 ug/ml in Feb’10 and 40 ug/ml in Apr’10 (1,800 vials available for each batch)

- Vast majority of the release and stability assays are fully validated
  Few assays need further validation (e.g., CCI, cGMP compliant bioassay)- to be completed in 2010

- Large-scale Lyo DP manufacturing is planned
  Manufacturer selected for large scale Mfg. of Lyo DP (135,000 3 cc vials per batch)
CBLB502 Final Drug Product (FDP)

What’s Left?

• Demonstrating extended stability of cGMP Lyo DP
• Completion of remaining assay validation
• Large scale Lyo DP mfg. and execution of the project to completion
• Addressing potential comments from FDA related to Lyo DP
Components of the Animal Rule

- **Human Safety**
- **Human Efficacy**
- **Animal Efficacy**
- **Animal PK**
- **Human PK**
- **Human Biomarkers**
- **Animal Biomarkers**

The diagram illustrates a feedback loop involving human safety, efficacy, and PK, as well as animal efficacy and biomarkers.
Phase Ia Clinical Trial Goals and Endpoints

- Determine safety range and pharmacological parameters of single IM doses
- Establish dose response of efficacy biomarkers
- Define recommended human dose based on comparison of biomarker response in humans and animals

CNS Comprehensive Phase One
(Miramar, Florida, USA)

- Experience: 14 years
- Number of beds: 120
- State-of-the-art 46,000 sq. ft.
- No 483’s
Phase 1a Trial Design

- Single-center, open-label, single-dose, escalating-dose, Phase 1 study
- Intra-muscular (IM) injection of healthy males or females aged 18 – 45 years
- Measured parameters: adverse events, safety labs, ECGs, pharmacokinetics (PK), pharmacodynamics (PD) of single IM doses of CBLB502 in human volunteers
- Cohorts-of-6 design to determine maximally tolerated dose (MTD) and dose(s) to take forward in development
- Only subjects with TLR-5^{WT/WT} enrolled
Phase Ia Data Collection and Analysis

Demographics

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<th>12</th>
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<th>35</th>
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Pharmacokinetics

Biomarker: IL6

Cleveland BioLabs, Inc
Phase Ia Conclusions

• Safety range of CBLB502 established
• Biomarker response mimics that of animal models
• Projected human efficacious dose estimated
• Profile of adverse events (AEs) characterized:
  ▪ Adverse event profile ("flu-like syndrome") was predictable and related to the known mechanism of action of CBLB502
  ▪ Majority of AEs were mild or moderate and transient (<2 – 4 hours)
    ▪ Rare and transient more serious AEs observed (generally resolve within 24 hours)
  ▪ Dose limiting toxicity was related to the known pharmacology of CBLB502 and was associated with a dose-related cytokine effects
  ▪ Adverse effect profile of CBLB502 is comparable to that of approved biologicals targeting immune system
Phase IIa Clinical Trial in Healthy Volunteers

- Nail down dose for definitive safety trial
- Demonstrate to FDA our knowledge of drug development process
- Reduce the number of subjects required for pivotal safety study
- Gather additional data on safety, PK, cytokine biomarkers in larger and broader subject population
- Completed enrollment May, 2009
- Last subject completed June, 2009
Phase IIa Clinical Trial Design

Healthy Volunteers → Randomize

R → CBLB502 25 µg IM  N = 25
A → CBLB502 35 µg IM  N = 25
N → Ibuprofen 400 mg po - 30 min → CBLB502 35 µg IM  N = 25
D → CBLB502 30 µg IM - 72 hr → CBLB502 30 µg IM  N = 25
O →
Phase IIa Trial: Timeline to Completion

- **LPI**
- **LPO**
- **DB Clean/Lock**
- **PK/AB Analysis**
- **Stats**
- **PK/Ab Report**
- **CSR**
What Do We Still Need to Do?
Definitive Safety Study of CBLB502

Study objectives

- Describe the adverse event profile of CBLB502 in healthy volunteers
- Describe the pharmacodynamic effects that characterize the mechanism of efficacy in animal models of radiation exposure
Proposed Safety Study Design

- Randomized
- Double Blind
- Placebo Controlled
- Multicenter
- Parallel Groups

Healthy Volunteers $\rightarrow$ Randomize

1. Placebo $\rightarrow$ AE, PD
2. CBLB502 $\rightarrow$ AE, PD