Cascade PRODRUG™

CPD100Li:

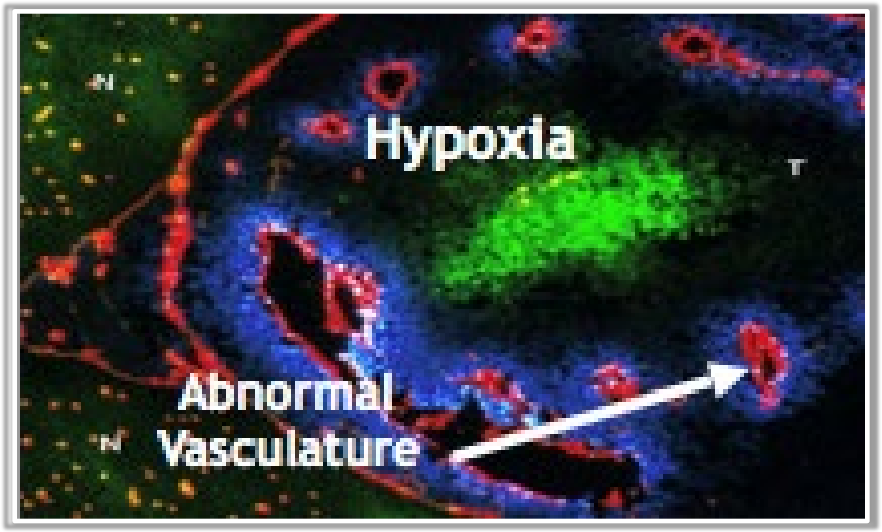
Unique Development Opportunity in Oncology

Cascade Background

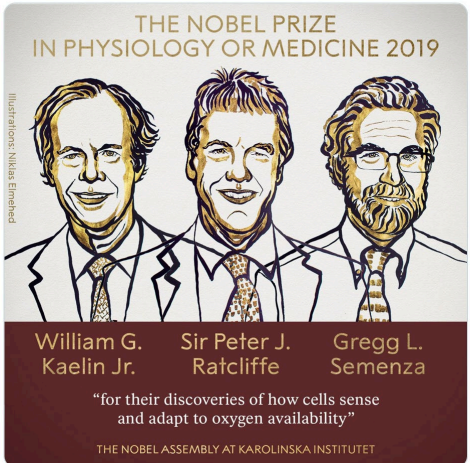
- CPD100Li (N-oxide prodrug of vinblastine) is a unique prodrug molecule that targets the hypoxic component of the tumor microenvironment
- Proof of Concept (POC) established for CPD100Li:
  - ✓ Prodrug SAR – In vitro microtubule polymerization inhibition assays
  - ✓ Bio-reduction under hypoxic conditions – Ex vivo cell based assays
  - ✓ 10X MTD & reduced side-effects – In vivo safety pharmacology
  - ✓ Strong anti-tumor response – In vivo efficacy models of pancreatic, lung and colon cancer
- Pancreatic cancer identified as initial indication – FDA Orphan Drug Designation
- Compelling evidence supporting development as single agent and/or in combination with other chemotherapy or checkpoint inhibitors
- IND filing targeted for 2025
- Cascade ProDrug (Based in Eugene, OR) – Platform chemistries for generating novel classes of hypoxia activated prodrugs and optimized formulation

Targeting the Hypoxic Tumor Microenvironment

Solving chemo and I/O ineffectiveness



Bernsen et al, (2000) J. Neurosurgery 93:449-454



J Clinical Invest 2020 Jan 2;130(1):4-6.

The 2019 Nobel Prize honors fundamental discoveries in hypoxia response

Hypoxia is a common feature of the tumor microenvironment that negatively impacts the effects of chemotherapy or immuno-oncology (I/O) treatment

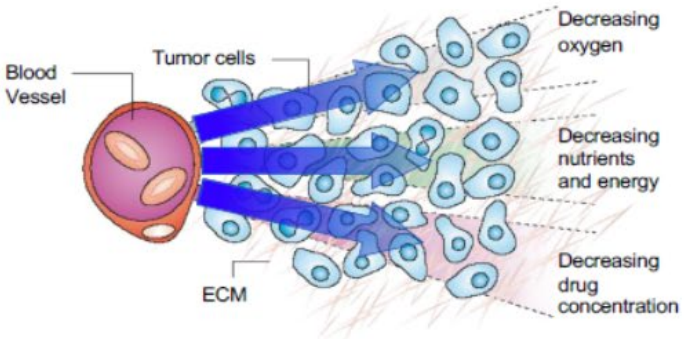
Hypoxia effect on tumor microenvironment

Solving chemo and I/O ineffectiveness

HYPOXIA: LOW OXYGEN (O_2) LEVELS

Solid tumors develop unique hypoxic tumor microenvironments

- Enhances aggressive tumor growth behavior
- Supports resident and infiltrating immunosuppressive cells
- Leads to exclusion and dysfunction of cytotoxic T cells
- Tumor mobility; induces Epithelial-to-Mesenchymal transitions



Tumor O_2 levels rapidly decrease as distance from blood vessel increases

Tumor microenvironment is a major impediment to conventional vinca alkaloid therapies

- Confers radiotherapy resistance
- Confers chemotherapy resistance
- Promotes malignant tumor cell phenotype
- Acidity reduces maximum possible drug dosing

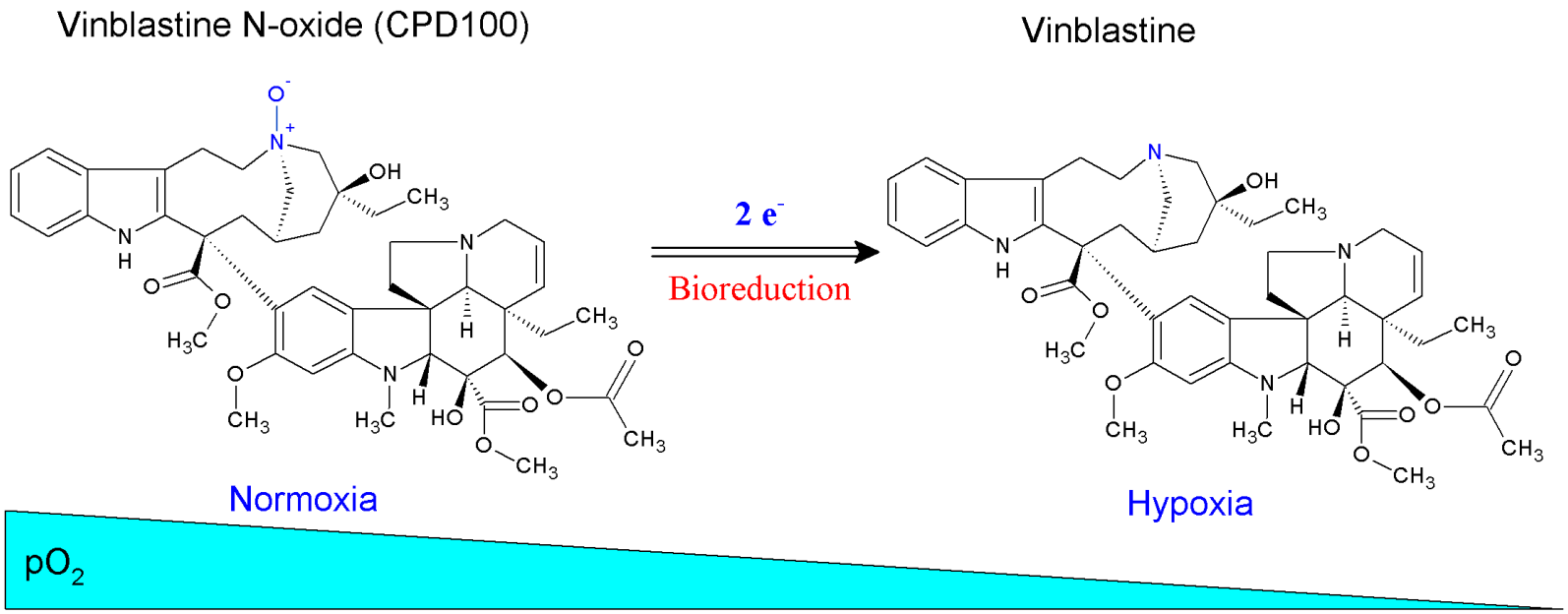
Hypoxia a common feature of most tumors

pO2 (oxygen partial pressure) measured in mmHg using electrode probes

Tumor	Tumor Tissue pO2 mm Hg (# patients)	Normal Tissue pO2 mm Hg (# patients)
Pancreas	2 (8)	57
Brain	13 (104)	26
Head & Neck	10 (592)	N/A
Lung	16 (26)	N/A
Breast	10 (212)	52
Cervix	9 (730)	42
Liver	6 (4)	30
Prostate	2-21 (57,55,55,10,13)	N/A
Sarcoma	14 (283)	51
Melanoma	12 (18)	41
Lymphoma	18 (8)	N/A

Vaupel, P. *et al.,* Antioxidants & Redox Signaling, ***9***: 1221, 2007

CPD100 Pro-Drug Chemistry



- **N-oxide prodrug technology inactivates parent drug with addition of oxygen; effecting SAR**
- **Reduction under hypoxic tumor environment releases oxygen and activates parent drug**
- **Alters the TME due to its cytotoxicity in hypoxic physiology**
- **Results in higher therapeutic index:**
  - ✓ **less normal tissue toxicity**
  - ✓ **higher MTDs in vivo**
  - ✓ **selective accumulation of activated cytotoxic drug in hypoxic tumor tissue**
  - ✓ **effective tumor cell killing**

Clinical POC for a hypoxia-activated prodrug

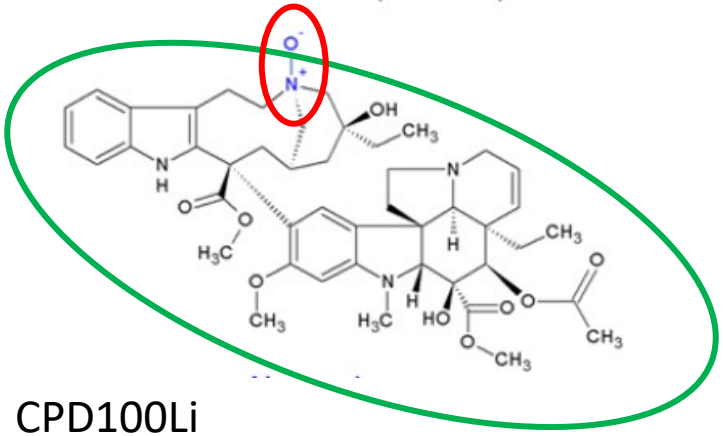
Evofosfamide vs Abraxane Pancreatic Phase III results

Trial Design	Overall Survival (OS)	Progression Free Survival (PFS)	Overall Response Rate (ORR)
Evo + Gem vs Placebo/Gem (n=660)	8.7 vs 7.6 months P=0.059 (not statistically significant)	5.5 vs 3.7 months P=0.004	15% vs 9% P=0.009
Abraxane + Gem vs Placebo/Gem (n=861)	8.5 vs 6.7 months P<0.001	5.5 vs 3.7 months P<0.001	23% vs 7% P<0.001

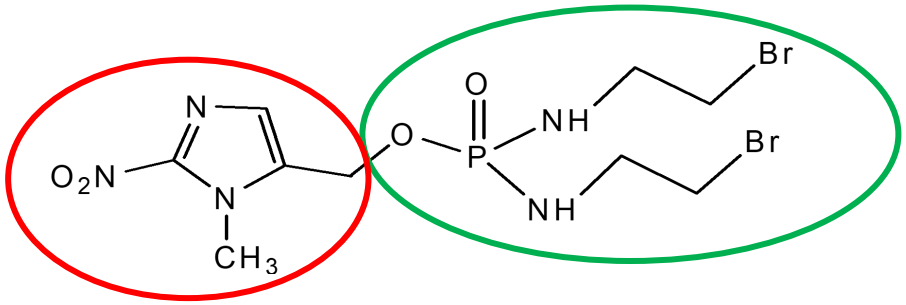
- **While Evofosfamide plus Gemcitibine just missed OS endpoint, data supports the demonstration of clinical POC for hypoxia-activated prodrug approach.**
- **Abraxane plus Gemcitibine data demonstrate the bar remains low for approvals in pancreatic cancer.**

CPD100Li vs Evofosfamide (THLD prodrug)

Vinblastine N-oxide (CPD100)



Evofosfamide



CPD100Li

Warhead: = Vinblastine (green)

Warhead MOA: blocks spindle formation

Prodrug Trigger: N-oxide (red)

Direct activation in cytosol

Liposomal Formulation (improved $t_{1/2}$, and tumor penetration)

Evofosfamide

Warhead: bromo ifosfamide (green)

Warhead MOA: DNA alkylator

Prodrug Trigger: nitroimidazole (red)

Involves free radical formation and activation in cytosol then translocation to nucleus

No Lipo formulation

CPD100Li features are uniquely differentiated from Evofosfamide and represent an opportunity for improved efficacy.

Why Vinblastine as Prodrug Warhead?

- Very potent cytotoxin targeting actively dividing cells; wide spectrum of tumor activity in humans
- Well understood and simple MOA
- FDA approved drug for treatment of cancer; 60+ years of clinical experience
- Drug chemistry amenable to inactivation with N-oxide formation and activation in hypoxic tumor environment

CPD100Li Overcomes TME Limitations to Treatment Effectiveness

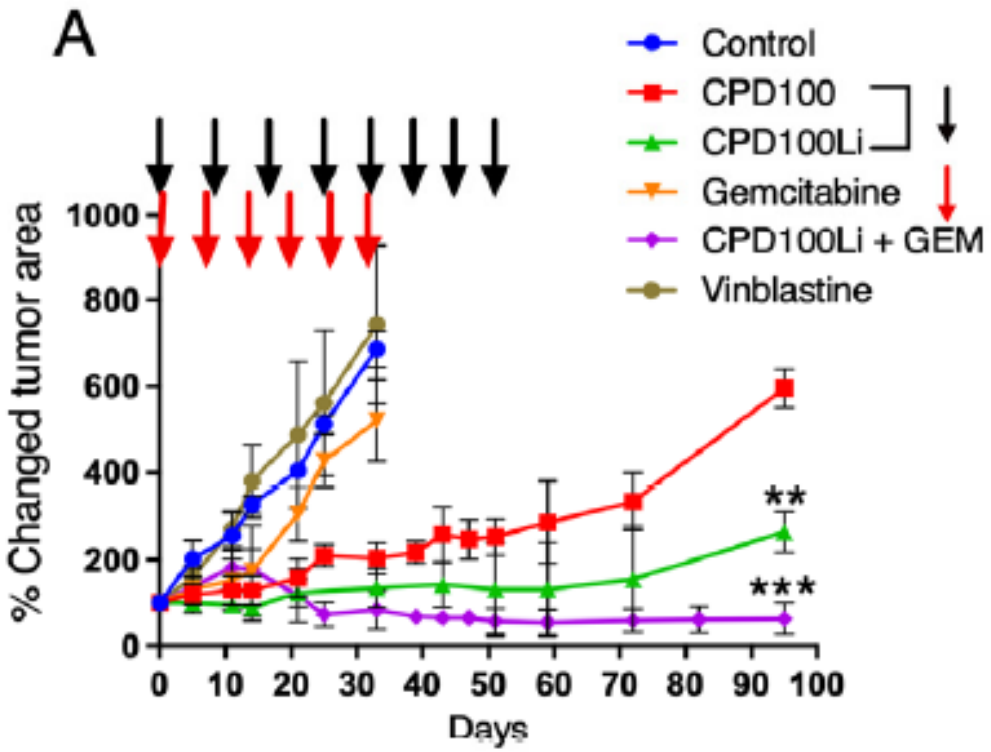
- Anti-tumor activity of all chemotherapy and checkpoint inhibitors are impaired by the tumor hypoxic microenvironment:
  - Abnormal leaky vasculature and poor lymphatic drainage
  - Low pH
  - Immunosuppression
  - Increased extracellular matrix (ECM) deposition and crosslink

- CPD100Li's is designed to remove TME limitations of current checkpoint inhibitors and chemotherapy:
  - Prodrug: inactivate warhead and introduce activatable trigger
  - Liposome Formulation: Enhance pharmacology; increase $t_{1/2}$, target and penetrate tumor and increase tumor retention
  - Remodel TME: activate in hypoxic regions; selectively kill cancer and immunosuppressive cells, reduce abnormal ECM and block epithelial-to-mesenchymal transition

CPD100Li Delivers Safer More Effective Therapy

CPD100Li Efficacy in Pancreatic Cancer Model

Human Panc-1 orthotopic model, Mono and Combo Therapy



Dosing regimen:

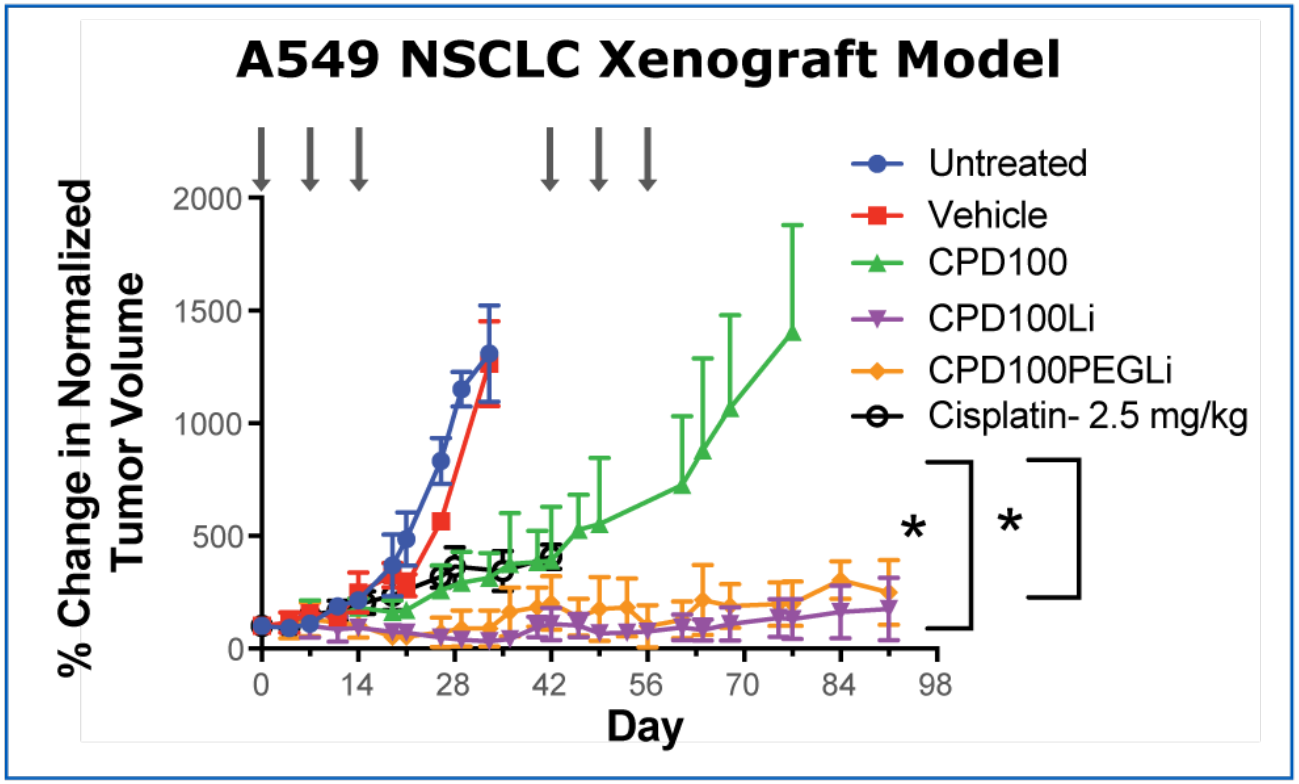
- **CPD100 and CPD100LI at 40mg/kg weekly for eight cycles**
- **GEM at 100 mg/kg biweekly six cycles**
- **Vinblastine at 5 mg/kg eight cycles**
- **CPD100LI at 40mg/kg weekly for eight cycles and GEM at 100 mg/kg biweekly six cycles**

CPD100Li is active as monotherapy and in combination with gemcitabine in Panc-1 model

Microfluidics Formulated Liposomes of Hypoxia Activated Prodrug for Treatment of Pancreatic Cancer
Pharmaceutics 2022, 14, 713

CPD100Li Efficacy in Human Lung Cancer Model

A549 NSCLC Xenograft, Mono Therapy

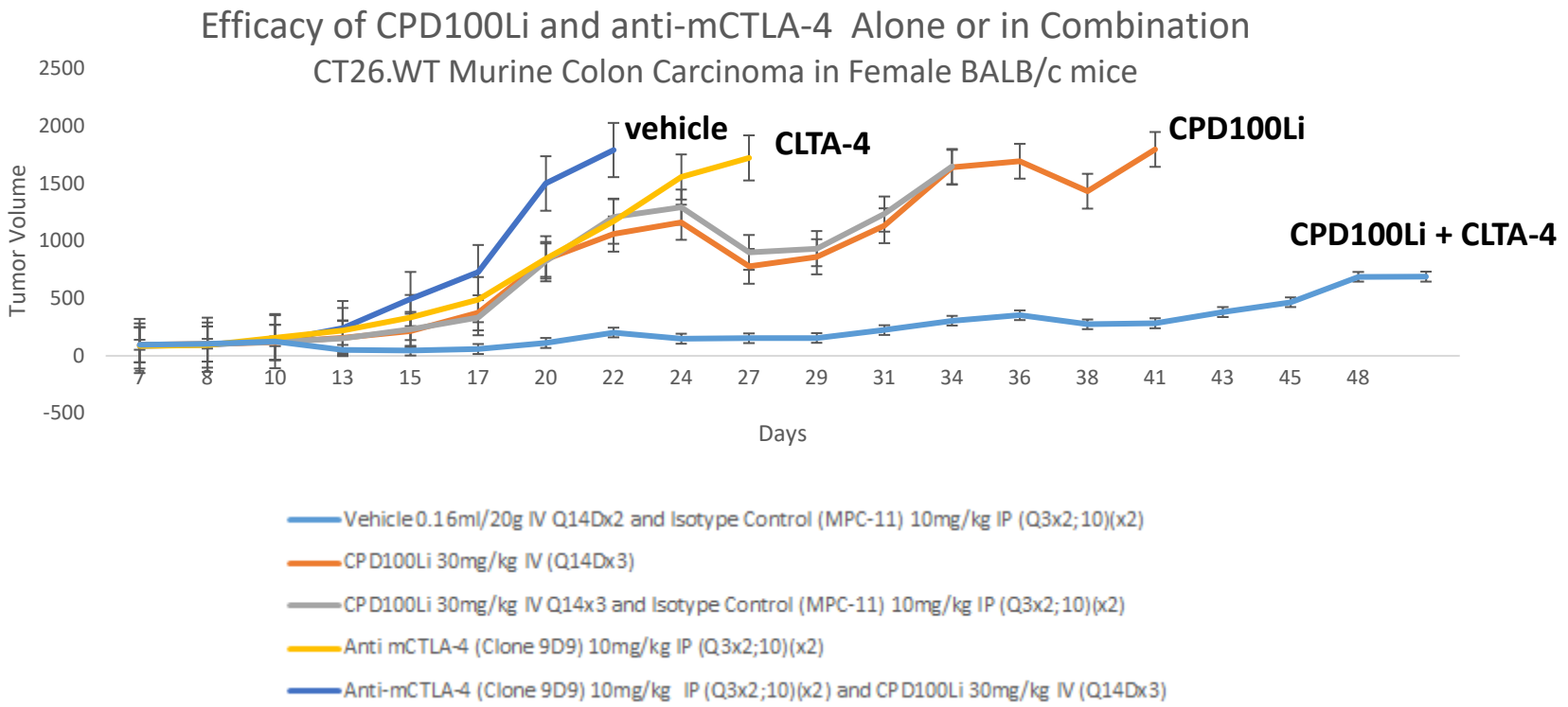


- *CPD100 dosed at 40 mg/kg (iv) in all on-treatment cohorts*
- *Cisplatin dosed at 2.5 mg/kg (MTD)*

Prolonged tumor growth inhibition with CPD100Li monotherapy

CPD100Li Efficacy in Syngeneic Colon Cancer Model

CT26.WT Murine Colon Carcinoma in Female BALB/c mice, Mono and Combo w/CTLA-4



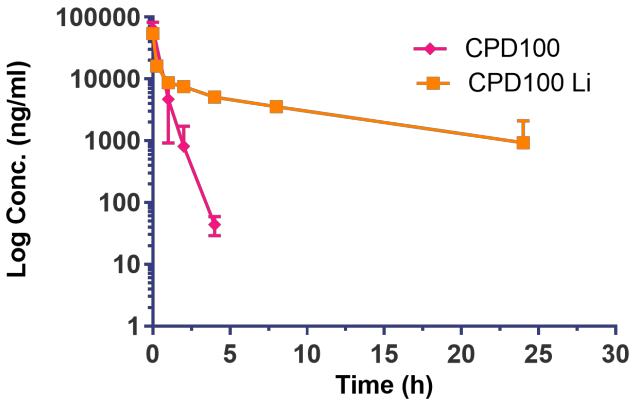
CPD100Li demonstrated strong synergistic response in combination with anti-CTLA-4

- ✓ **Significant prolonged tumor growth inhibition vs CTLA-4 or CPD100Li alone**
- ✓ **Higher M1/M2 ratio suggests lowered tumor inhibitory environment and better prognosis**

CPD100Li Formulation & Pharmacokinetics
Optimized Lead Prodrug

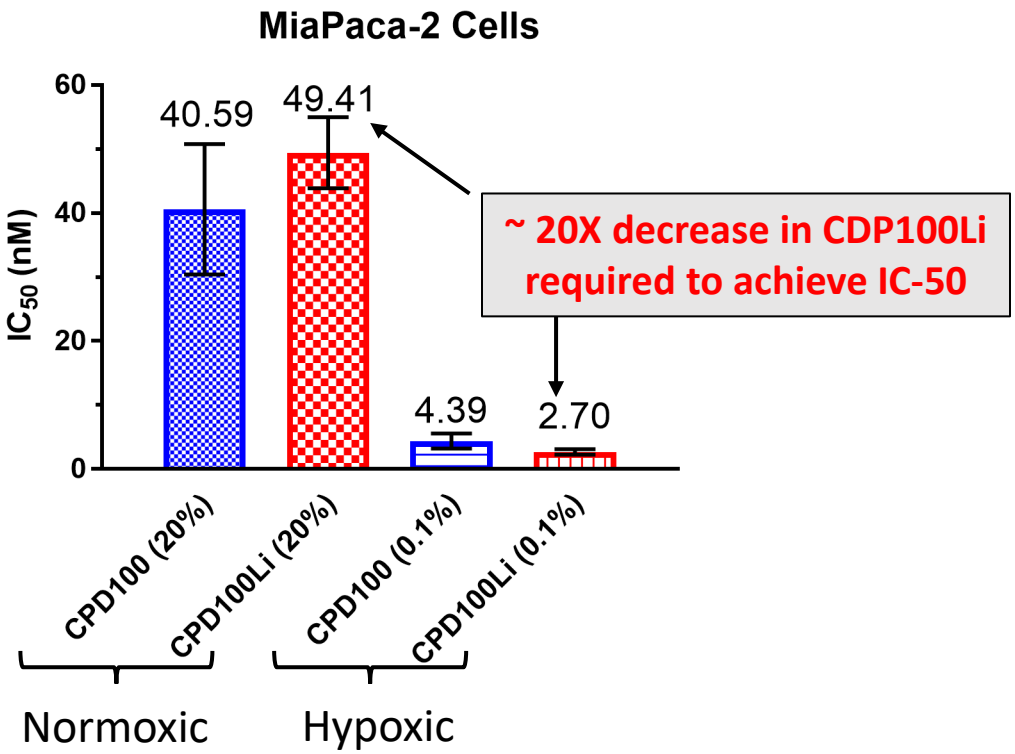
Composition – Lipids
- SMP: Egg-Sphingomyelin (55%)
- Chol: Cholesterol (45%)
- A23187

Liposome Characteristics
- Size: 153.9 ± 2.7 nm
- POI: 0.07 ± 0.01
- Drug Loading: 5.05 ± 0.08 mg/mL



CPD100Li is well tolerated
- ✓ No acute toxicities observed (MTD = 40 mg/kg)
  >10X greater MTD than vinblastine
- ✓ No weight loss in tumor-bearing mice on treatment
- ✓ Modest elevations of liver enzymes and hematological markers

CPD100Li Activation in Hypoxic Environment



CPD100Li significantly more active against tumor cells under hypoxic conditions

Summary

- Hypoxia is a feature of most solid tumors and impediment to conventional therapies – prodrug approach uniquely targets tumor microenvironment

- CPD100Li represents a unique pro-drug molecule with validated warhead (vinblastine) initially targeting pancreatic cancer
  - ✓ Potentially multiple pathways for development in other hypoxic tumors

- Compelling data in-vivo:
  - ✓ As a single agent
  - ✓ In combo with chemotherapy (Gem) and check point inhibitor (anti CTLA-4)
  - ✓ Activity seen in pancreatic, lung and colorectal cancers

- Cascade considering partnerships to advance development of CPD100Li

Cascade PRODRUG™

END OF PRESENTATION

Al Cochrane: Chairman & CEO (agcochrane@comcast.net)
Eric Malek: CBO (ericmalek@gmail.com)