



ALTERED ENERGY METABOLISM DIRECTED (AEMD) COMPOUNDS

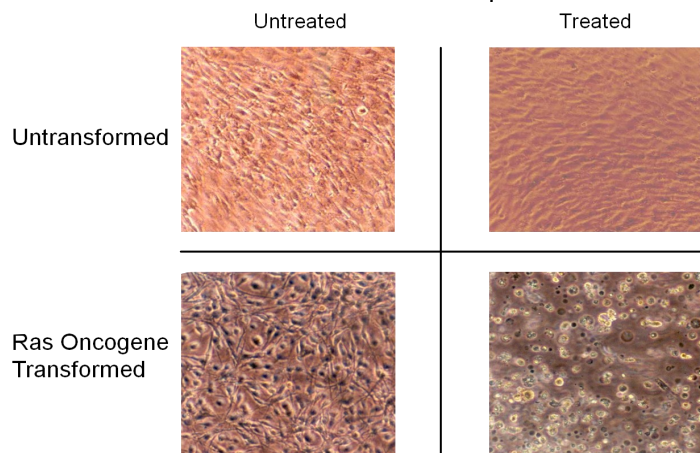
It has been long recognized that cellular energy production in many cancer types is distinct from energy production in healthy cells. This altered cancer cell energy metabolism is considered to be a hallmark of the transformation of normal cells to cancerous cells and presents an attractive target for the development of novel and potentially selective and broadly applicable interventions for the treatment of cancer. This bioenergetic distinction between tumor cells and normal tissues is currently being exploited to provide enhanced imaging, diagnosis and staging of tumors in humans via Positron Emission Tomography (PET) imaging.

Cornerstone's proprietary AEMD small molecule compounds are believed to exploit the aberrant energy metabolism of cancer cells and its link to pathways controlling cancer cell growth, development, apoptosis and necrosis. CPI-613, the lead product candidate from the Company's AEMD platform has undergone extensive *in vitro* and *in vivo* anti-tumor studies as well as animal toxicology studies which have demonstrated highly desirable characteristics that strongly warrant clinical evaluation of these agents in humans. CPI-613 is being evaluated as a single agent therapy in Phase I/II clinical trial in multiple cancers in both the United States and Canada. The US FDA has also granted Orphan Drug Status to CPI-613 for the treatment of pancreatic cancer. Accordingly, the Company has initiated a Phase I/II trial in combination with gemcitabine for newly diagnosed pancreatic cancer patients or those with tumors intended to be treated with gemcitabine.

Among the more salient AEMD compound characteristics observed in the preclinical setting are:

- ◆ A high degree of cancer cell selectivity
- ◆ Broad spectrum activity against a wide variety of cancer cell lines representing different genetic mutations, including cancer cell lines characterized as being multiple drug resistant
- ◆ A high degree of tolerability in animal models resulting in an unusually significant therapeutic index

NIH-3T3 cells are a quasi-normal cell line that do not produce tumors in experimental animals and exhibit contact-inhibition of growth in cell culture. Introduction of the mutant *ras*-oncogene into this cell line produces transformed cells which produce tumors in experimental animals and exhibit uncontrolled growth in culture, providing an especially well-controlled model for testing the cancer specificity and effectiveness of the AEMD compounds.



Shown are untransformed (upper panels) and ras-transformed (lower panels) NIH-3T3 cells that have either been treated with an AEMD compound (right hand panels) or left untreated (left hand panels) for 24 hours. As shown in the lower right panel, the AEMD compound kills the malignant, ras-transformed cells while leaving the contact-inhibited non-transformed NIH-3T3 cells (upper right panel) apparently unaffected. Within another 24-36 hours all the AEMD compound treated ras-transformed cells were dead while the AEMD compound treated untransformed cells remain alive.

BROAD SPECTRUM ACTIVITY OF AEMD COMPOUNDS

Cornerstone has evaluated the activity of its AEMD compounds against a wide array of established cancer cell lines in cell culture, including those representing some of the most difficult to treat cancer types as well as cancer cell lines characterized as multiple drug resistant. In all cases, the tested cell lines were 100% killed by the AEMD compounds within the same AEMD compound concentration range. Cells derived from non cancerous tissues were also tested and were apparently unaffected by the AEMD compounds even at concentrations that are several fold higher than that at which cancer cells from the same tissue of origin are killed as shown in the *In Vitro* Anticancer Activity table. CPI-613 activity was also evaluated in the EDR[®] Assay offered by Oncotech, Inc. The EDR[®] Assay is an *in vitro* drug resistance assay that identifies patients that will not respond to a cancer therapeutic with > 99% accuracy. The assay uses disaggregated cells from individual human tumor specimens to assess their *in vitro* responsiveness to various anticancer drugs and can also be used to evaluate the activity of novel agents such as CPI-613. In the CPI-613 study, tumor specimens from cancer patients diagnosed with either lung, breast, pancreatic or colon cancer (5 different specimens per cancer type) were exposed to CPI-613 at various concentrations and assessed for their responsiveness in the EDR[®] assay. All tumor cells tested were completely inhibited by CPI-613 in this study. Shown below is a sampling of the results from the EDR[®] study comparing the responsiveness of patient tumor cells to either CPI-613 or anticancer agents (control) typically used to treat patients with the specified cancer type.

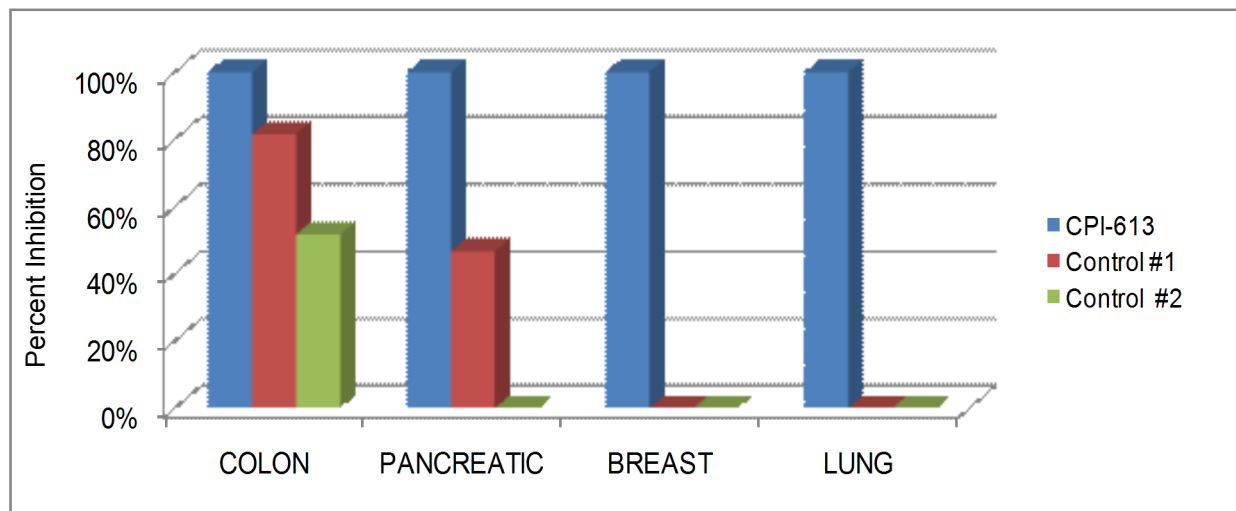
In Vitro Anticancer Activity

ORIGIN OF CANCER CELLS	CELL LINE(S)	ACTIVITY (CELL KILL)
BONE osteosarcoma	Saos-2	Active
BRAIN glioblastoma	U87MG, SF539	Active
BREAST adenocarcinoma	MCF-7, MDA 543, SK-Br-3	Active
CERVICAL carcinoma	HeLa	Active
COLORECTAL carcinoma	SW480	Active
LEUKEMIA	MV-4-11, HL60, JURL	Active
LIVER carcinoma	HepG2	Active
LUNG carcinoma (NSCLC)	A549, H460	Active
LUNG carcinoma (SCLC)	NCI/H69	Active
MUSCLE rhabdomyosarcoma	RD	Active
OVARIAN carcinoma	SK-OV-3,	Active
OVARIAN adenocarcinoma	A2780	Active
PANCREATIC adenocarcinoma	BxPC-3, AsPC-1	Active
PROSTATE carcinoma	Ln Cap	Active
SKIN melanoma	SK-MEL-28	Active
UTERINE sarcoma	MES-SA	Active

ORIGIN OF RESISTANT CELLS	CELL LINE(S)	ACTIVITY (CELL KILL)
LUNG carcinoma (SCLC)	H69AR	Active
OVARIAN adenocarcinoma	A2780Dx, NCI/ADR-RES*	Active
UTERINE sarcoma	MES-SA/MX2	Active

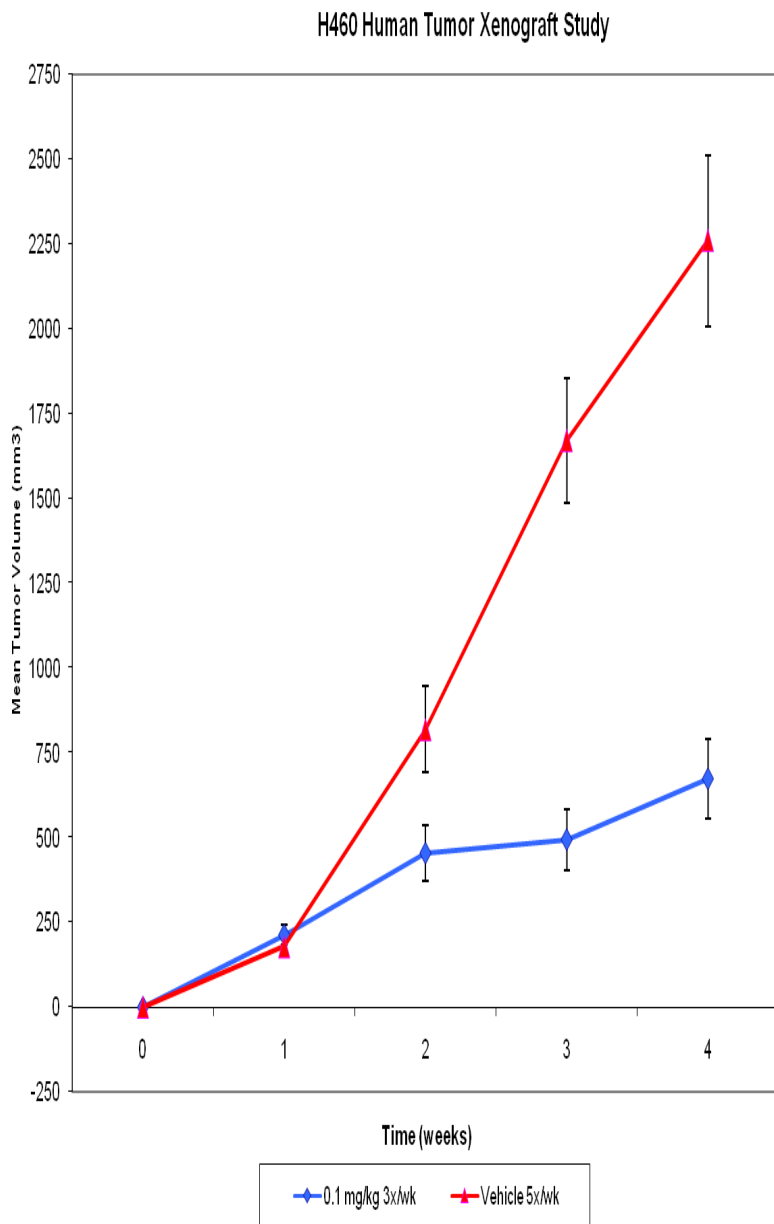
ORIGIN OF NORMAL CELLS	CELL LINE(S)	ACTIVITY (CELL KILL)
BREAST mammary epithelium	HMEC	Inactive
LUNG small airway epithelium	SAEC	Inactive
SKIN keratinocytes	NHKC	Inactive

* Previously characterized as a resistant breast cancer cell line derived from MCF-7



Control #1	5FU	5FU	Cisplatin	Cisplatin
Control #2	Irinotecan	Gemcitabine	Paclitaxel	Paclitaxel

AEMD COMPOUND IN VIVO TOLERABILITY



CPI-613 has been studied in human tumor xenograft mouse models to evaluate its ability to inhibit tumor growth. Shown here are the results of such a study using the aggressively growing H460 human non-small cell lung cancer cell line. H460 cells implanted in mice were allowed to grow to an average size of approximately 200mm³ prior to the initiation of dosing with CPI-613. The mice were subsequently dosed either with CPI-613 intraperitoneally (IP) at a dose level of 0.1mg/kg three times per week (n=8). Weekly change in tumor volume of each group was measured and compared to the vehicle control group (n=8) as presented here. While effectiveness in inhibiting tumor growth was observed at dose levels as low as 0.1 mg/kg, dose levels of 100 mg/kg have been well tolerated in tumor bearing mice, implying an unusually high therapeutic index for a small molecule anticancer agent. Error bars are +/- SEM.

INTELLECTUAL PROPERTY

The AEMD compound platform is covered by both US and ex-US patents licensed on a worldwide, exclusive basis to Cornerstone Pharmaceuticals with additional Cornerstone owned composition of matter patent applications under review and preparation.