1000

Targeting Lipid Rafts in Hypoxic Pancreatic Ductal Adenocarcinoma: Preclinical Evaluation of [225Ac]CLR 121225, a Novel Actinium-Based Radio-Conjugate

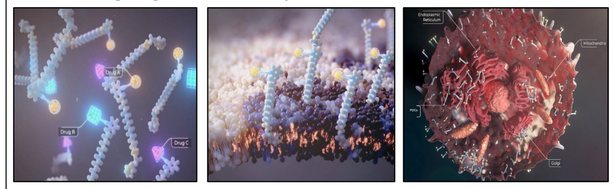
Authors: Randall Hoover, Maria Banach and Jarrod Longcor
Cellectar Biosciences, Florham Park NJ

Introduction

Advanced pancreatic ductal carcinoma (PDAC) has a 5 year survival of <10%. PDACs exhibit dense desmoplasia due to abnormal accumulation of extracellular matrix and proliferative fibroblasts, resulting in hypovascularity and a hypoxic environment requiring the tumor cells to use lipids from the microenvironment. Lipid rafts (LR) are highly ordered membrane microdomains that transport lipids into the cell. LRs are generally enriched in tumor cells and even more so in hypoxic environments. Here, we disclose [225Ac]CLR 121225 (CLR 225), a novel actinium-based radio-conjugate uniquely designed to target LRs and enter the tumor cell.

Figure 1: PDC Mechanism of Action

Universal Targeting With Diverse Payloads



(1) PDC containing desired payload with tumor-targeting phospholipid ether

(2) Specific targeting of lipid raft on cancer cell membrane

(3) Intercellular delivery of payload by transmembrane flipping of lipid raft

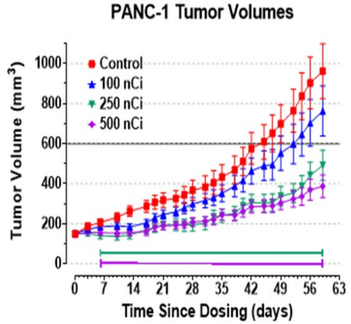
Study Summary

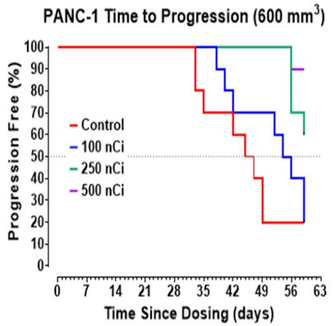
PANC-1, MIA PaCa-2 human pancreatic carcinoma cells (ATCC), or BxPC-3 tumor fragments were implanted subcutaneously in the right high axilla of female nude mice. Once tumor volumes of 150mm^3 were achieved, the mice were randomized to control and treatment groups (n=10 per group for each cell type). PANC-1 and MIA PaCa-2, animals received single IV doses of either vehicle (controls), 100, 250 or 500 nCi of CLR225. BxPC-3, animals received single IV doses of either vehicle, 250 or 500 nCi, or 2x500 nCi on Day 0 and Day 14. Tumor volumes were measured by caliper and body weights recorded.

For all 3 models, the CLR225 treatments were well tolerated with no deaths in the treatment windows and body weight changes within acceptable limits.

PANC-1

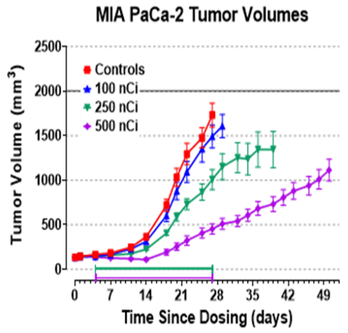
- CLR225 SD IV at 100, 250 or 500 nCi, caused an approximate 14 day delay in tumor growth.
- Significant differences in tumor volumes were observed for the 250 and 500 nCi groups vs controls
- Time to a tumor volume of 600 mm^3 was significantly increased for 250 and 500 nCi. Median time to 600 mm^3 was not reached for the 250 and 500 nCi groups, vs 46 days for controls.

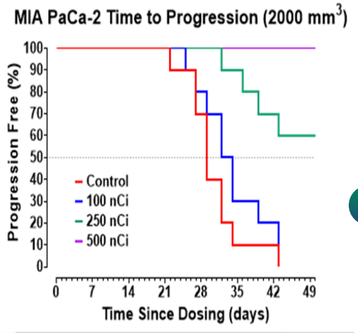




MIA PaCa-2

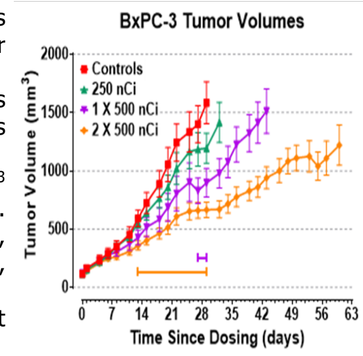
- CLR225 SD, IV at 250 or 500 nCi, caused an approximate 14 day delay in tumor growth.
- Significant differences in tumor volumes were observed for the 250 and 500 nCi groups vs controls.
- Time to a tumor volume of 2000 mm^3 was significantly increased vs controls for the 250 and 500 nCi groups. Median time to 2000 mm^3 was not reached for the 250 and 500 nCi groups, vs 29 days for controls.

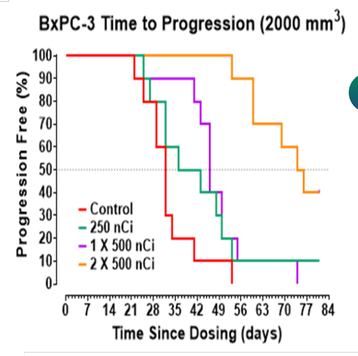




BxPC-3

- IV at SD 500 nCi, or 2x500 nCi doses spaced 14 days apart, inhibited tumor growth.
- Significant differences in tumor volumes were observed for all treatment groups vs controls.
- Time to a tumor volume of 2000 mm^3 was significantly increased vs control. Median times to 2000 mm^3 for controls, 250, 1 × 500, and 2 × 500 nCi were 32, 39.5, 46, and 75 days, respectively.
- Multiple doses provided a clear benefit over a single dose



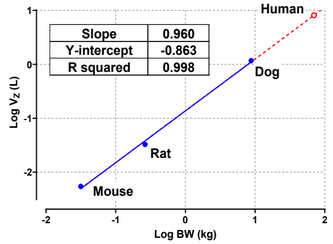


Pharmcokinetic Studies

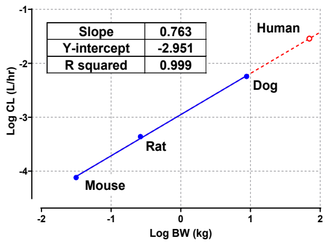
CLR 121225 (unlabeled) PK was tested in male and female mice, rats and dogs. Single IV bolus doses of 0.01 (rat and dog only), 0.1 and 1 mg/kg were given. In all 3 species, the volume of distribution indicated limited distribution. Exposures were close to dose proportional. Differences in PK between males and females were not significant in mice and rats, whereas in dogs clearance was slightly higher in females. Urinary excretion of unchanged drug in rats and dogs was very low, <0.5 % of dose.

Allometric analysis predicted a volume of distribution in a 70 kg human of about 8 L and a terminal half-life of 196 hr.

Vz



CL



Toxicity Studies in Dog

CLR 121225 (unlabeled) was tested in a GLP-compliant toxicity study in male and female dogs. IV doses at 0.1, 1 and 4 mg/kg were given q14d for a total of 4 doses (6 weeks). All animals survived to their scheduled sacrifice. No CLR 121225-related veterinary observations; ophthalmic observations; alterations in body weight or food consumption; ECG effects; hematology, coagulation, clinical chemistry, or urinalysis effects; organ weight changes; or macroscopic or microscopic observations were noted.

Conclusions

- CLR225 demonstrated meaningful inhibition of tumor growth and potential survival benefit in 3 mouse pancreatic cancer xenograft models.
- PK studies of CLR121225 (unlabeled) in mice, rats and dogs indicated predictable behavior, dose-linearity, with similar results in males and females.
- In a GLP multiple-dose toxicity study in dogs, demonstrated no toxicities.