AUPM-170: First-in-Class, Oral Immune Checkpoint Inhibitor of PD-L1/2 and VISTA

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ABSTRACT

Highly durable clinical responses observed with antibodies to immune checkpoint receptors such as CTLA4 and PD1 have revolutionized the outlook of cancer therapy. However, while these antibodies show impressive clinical activity, they suffer from the shortcomings including 1) lack of response in the majority of patients, 2) the need to administer by intravenous injection, and 3) immune-related adverse events due to the breaking of immune self-tolerance. Sustained target inhibition as a result of a long half-life (>15-20 days) and >70% target occupancy for months are likely contributing to irAEs observed.

Herein we report the discovery of the first-in-class small molecule AUPM-170, a PD-L/VISTA dual antagonist that is amenable for oral dosing, shows the potential to lead to greater response rate due to dual antagonism and with a shorter pharmacokinetic profile as a strategy to better manage irAEs. AUPM-170 exhibits functional specificity against PD-L1/2 and VISTA and no cross reactivity with other immune checkpoint pathways.

To achieve this focused specificity, a library of compounds mimicking the interaction of PD1 with PD-L1 was designed and synthesized. Screening and analysis of the resulting library led to the identification of compounds capable of functional disruption of the PD-L1/L2 and VISTA, a checkpoint protein with pockets of sequence similarity with PD-L1. Further optimization of the initial hits resulted in compound AUPM-170, with desirable physico-chemical properties and exposure upon oral administration.

The ability of AUPM-170 to disrupt PD-1/PD-L1/2 or VISTA interaction has been inferred though functional studies. AUPM-170 exhibits potent activity comparable to that of an anti-PD1 or anti-VISTA antibody when tested in assays to rescue lymphocyte proliferation and effector functions inhibited by PD-L1/L2 or VISTA. AUPM-170 did not rescue specific immune function readouts of leukocytes treated with CTLA4, TIM3, LAG3 or BTLA. Importantly, AUPM-170 exhibits sustained immune PD *in vitro* and in vivo suggesting that drug efficacy may extend beyond drug clearance. AUPM-170 exhibits *in vivo* efficacy in syngeneic pre-clinical models of melanoma, breast carcinoma and colon cancers. Significant efficacy in the inhibition of both primary tumor growth and metastasis was noted upon once a day oral dosing. In a 14-day repeated dose toxicity studies, the lead compound was well tolerated at >100x of the efficacious doses.

These findings demonstrate that the inhibition of the PD-L1/2 and VISTA pathways results in immune activation and anti-tumor activities which provide strong rational support for the further clinical development of AUPM-170. IND-enabling studies are currently underway which will advance AUPM-170 to the clinic.

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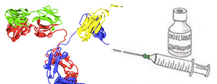
OBJECTIVES

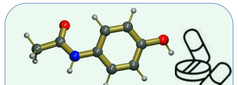
Small molecule immune checkpoint antagonists with the ability to block multiple immune checkpoint pathways. Candidates are designed and selected for the ability to disrupt the PD-1/PD-L1 checkpoint pathway plus one or more related pathways.

Competing Antibodies



- MW ~150,000 Da
- Recombinant production
- Higher cost of goods

Aurigene's small molecules

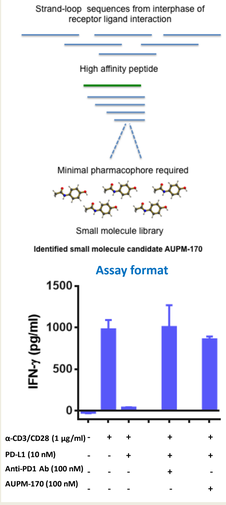


- MW <500 Da
- Synthetic production
- Lower cost of goods

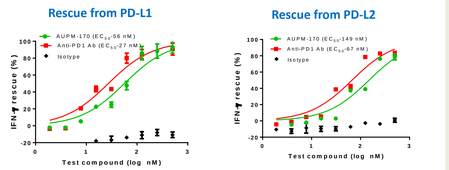
Property	Antibody	Our approach – small molecule
Effective population	Specific to target of interest (such as PD1)	Opportunity to expand beyond PD1/PD-L1
Pharmacokinetics	Long half-life (>15-20 days) likely contributing to irAEs observed	Short-acting agents for better management of adverse events
Route of administration	Large size- IV dosing needed	Making it orally available by substantial reduction in size

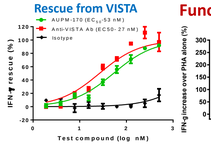
RESULTS

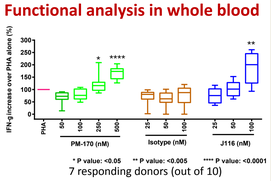
Strategy for lead identification



AUPM-170 rescues IFN-γ expression in human T cells from PD-L1, PD-L2 or VISTA inhibition





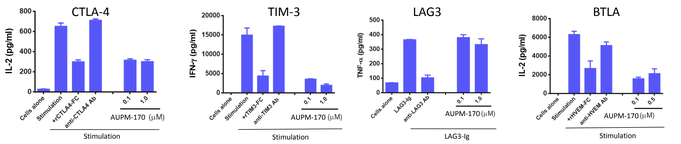


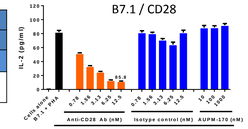
7 responding donors (out of 10)

AUPM-170 potently antagonizes PD-1 and VISTA pathway and enhances PHA-stimulated IFN-Y secretion in whole blood

RESULTS

AUPM-170 does not inhibit other immune checkpoints

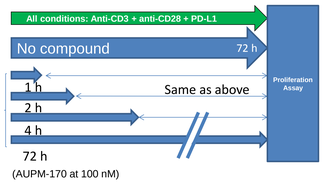


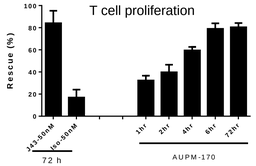


EC_{50} (nM)		Percent inhibition (%)							
PD-L1	VISTA	LAG-3		BTLA		CTLA-4		TIM-3	
		0.1μM	1μM	0.1μM	0.5μM	0.1μM	1μM	0.1μM	1μM
17 nM	37 nM	-4.2	9.0	0	0	4.8	0.8	-7.8	-22.9

No inhibition of other checkpoints tested and no off target effect on B7.1
(Also no inhibition of any of the targets in a CEREP panel of enzymes, receptors, ion channels)

Short exposure results in sustained PD *in vitro* in human T cells



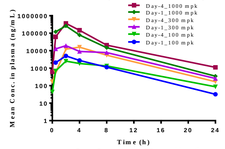


Short duration AUPM-170 exposure rescues T cells from PD-L1 inhibition

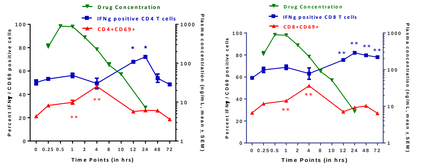
Pharmacokinetic profile of AUPM-170

Parameter	Mice	Rat	Dog
$AUC_{(0-t)}$ (μg*hr/ml) IV: mice and dog (1mpk) and rat (3 mpk)	1.32	4.18	4.82
Clearance ml/h/kg	12.6	11.9	3.5
$AUC_{(0-t)}$ (μg*hr/ml) PO at 10 mpk	3.45	3.88	22.5
Tmax (hr)	1.0	1.0	1.0
Cmax (μg/ml)	0.52	0.59	4.3
F (%)	26	30	46

Oral PK exposure in monkey

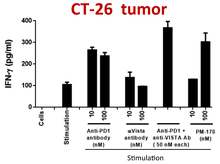


Exhibits a sustained immune PD *in vivo*



CD69 correlates with initial drug activity and IFN-Y correlates with the persistent PD

Activates T cells from CT-26 tumor

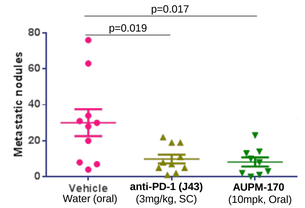


AUPM-170 enhances the activation of T cells from TILs

RESULTS

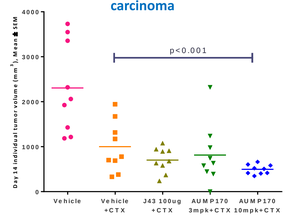
AUPM-170 exhibits anti-tumor efficacy in mice

AUPM-170 inhibits the establishment of lung metastasis of B16/F10 tumors



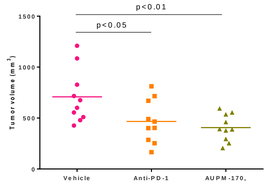
Day 13 post tumor cell inoculation
AUPM-170 dosed daily, anti-PD-1 dosed 1/week

AUPM-170 inhibits the growth of CT26 colon carcinoma



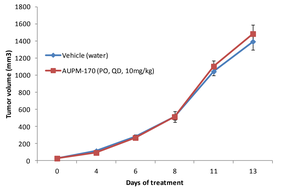
Day 12 post tumor cell inoculation. AUPM-170 dosed daily, anti-PD-1 dosed 1/week; CTX: Cyclophosphamide

AUPM-170 exhibits efficacy in MC-38 syngeneic colon carcinoma model



Day 12 post treatment (17 post tumor cell inoculation)
AUPM-170 dosed daily, anti-PD-1 dosed 1x/week

AUPM-170 does not exhibit MC-38 anti-tumor efficacy in immune deficient SCID-Beige mice



Toxicology summary of AUPM-170

Species	Study	Remarks
Mice (Balb/c)	Single Dose Maximum Tolerated Dose (MTD) Study	AUPM-170 was well tolerated up to the highest tested dose of 1000 mg/kg (limit dose)
	14 Days Repeated Dose Toxicity	No test item related toxicological effects observed up to the limit dose of 1000 mg/kg body weight/day
Monkey (cynomolgus)	MTD study- Escalating dose, once daily for 4 consecutive days	Dose levels of 100, 300, and 1000 mg/kg were well tolerated. There were no test article-related changes and MTD was not established. Showed dose proportional increase in systemic exposure from 100 to 1000 mg/Kg and showed no significant sign of induction or accumulation

SUMMARY

We have identified **AUPM-170**, a novel dual antagonist of PD-L and VISTA. AUPM-170 exhibits:

- Potent rescue of PD-L or VISTA mediated inhibition of T cell proliferation and IFN-γ production
- Desirable DMPK profile including oral bioavailability
- PD profile consistent with immune modulation *in vivo*
- Anti-tumor activity in multiple syngeneic tumor models

AUPM-170 exhibits flexible, oral administration and antagonism of PD-L and VISTA which may provide for improved or expanded clinical benefit in cancer patients.