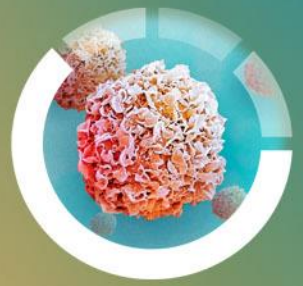
ORIC



OVERCOMING RESISTANCE IN CANCER

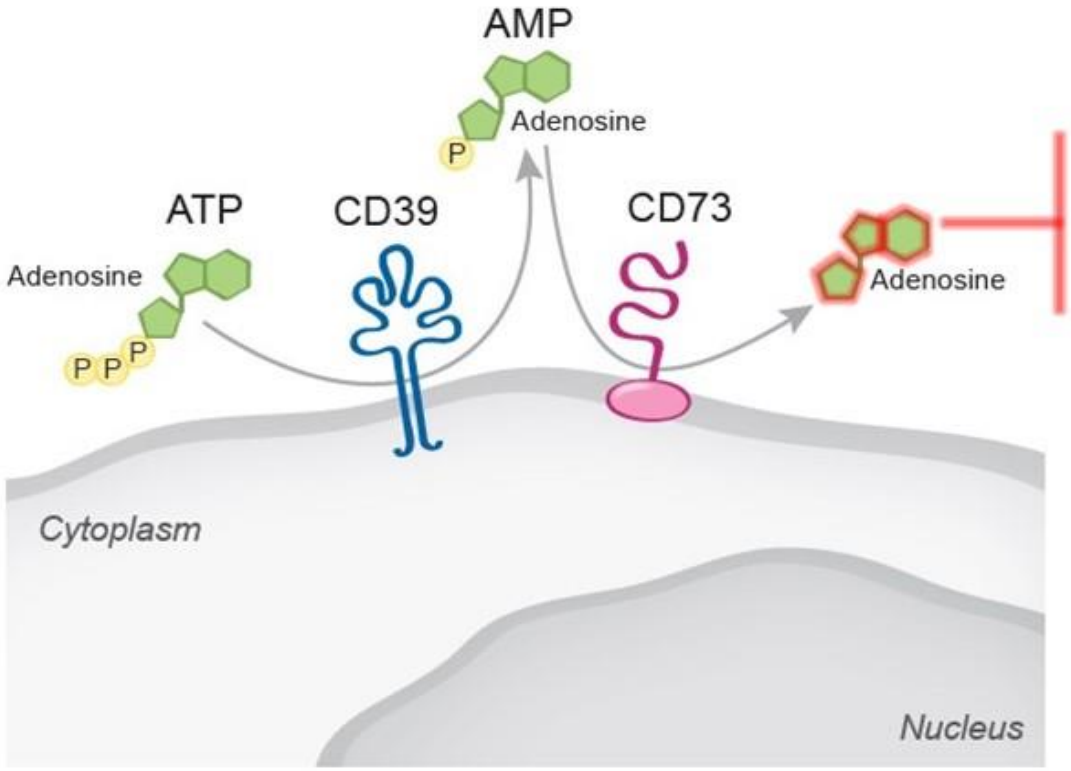
Orally Bioavailable Small Molecule CD73 Inhibitor Reverses Immunosuppression by Reduction of Adenosine Production (Abstract #1242)

Xiaohui Du
ORIC Pharmaceuticals
AACR Annual Meeting 4/2020

Disclosure

- Xiaohui Du is an employee of ORIC Pharmaceuticals

CD73 is required for adenosine production and linked to therapy resistance



- T cell priming
- T cell expansion
- T cell activation / cytolytic activity
- NK degranulation
- Macrophage M1 polarization
- DC maturation / activation

CD73

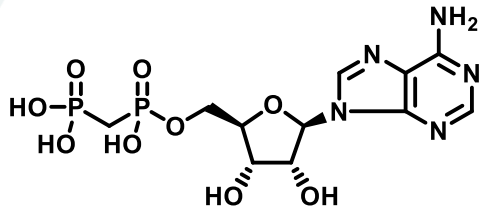
- Overexpressed across cancer types driving local elevation of adenosine
- Overexpression correlated with poor prognosis
- Mediates immunosuppression and chemoresistance via adenosine production

Therapeutic Hypothesis

- CD73 inhibition may enhance activity of chemotherapy and immunotherapy
- Small molecule approach may differentiate in dosing regimen and tumor penetration

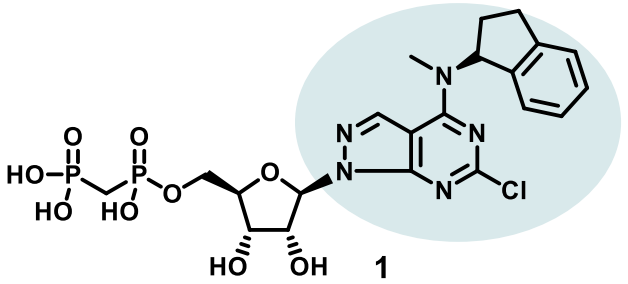
Surveying linker region towards *exo* phosphonate led to novel starting point

Müller *J. Med. Chem.* **2015**, *58*, 6248.



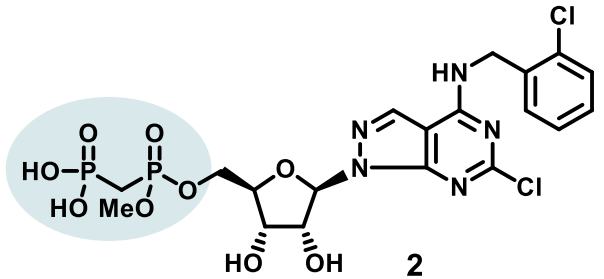
AOPCP

Biochem IC_{50} : **2996** nM
Rat PO : *No oral exposure*



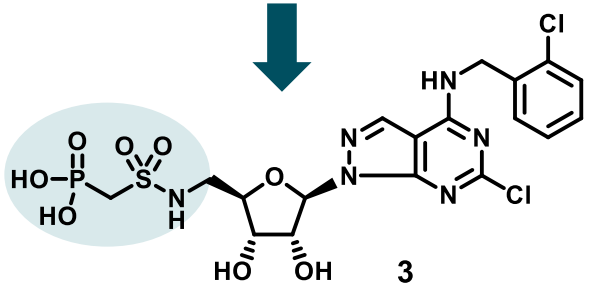
1

Biochem IC_{50} : **0.52** nM
Rat PO : *No oral exposure*



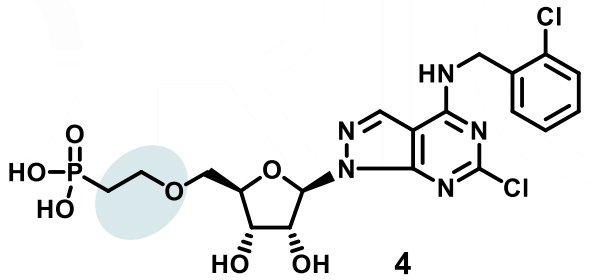
2

Biochem IC_{50} : **25** nM
Rat PO C_{max} : **0.12** µM
Rat PO AUC_{inf} : **0.56** µM*hr



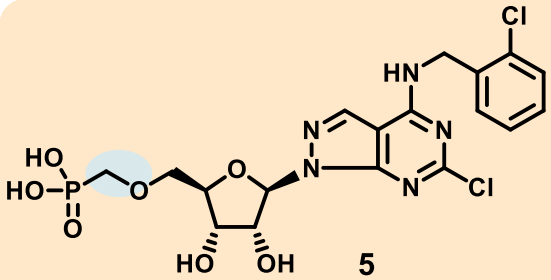
3

Biochem IC_{50} : **328** nM
Rat PO C_{max} : ND
Rat PO AUC_{inf} : ND



4

Biochem IC_{50} : **88** nM
Rat PO C_{max} : ND
Rat PO AUC_{inf} : ND

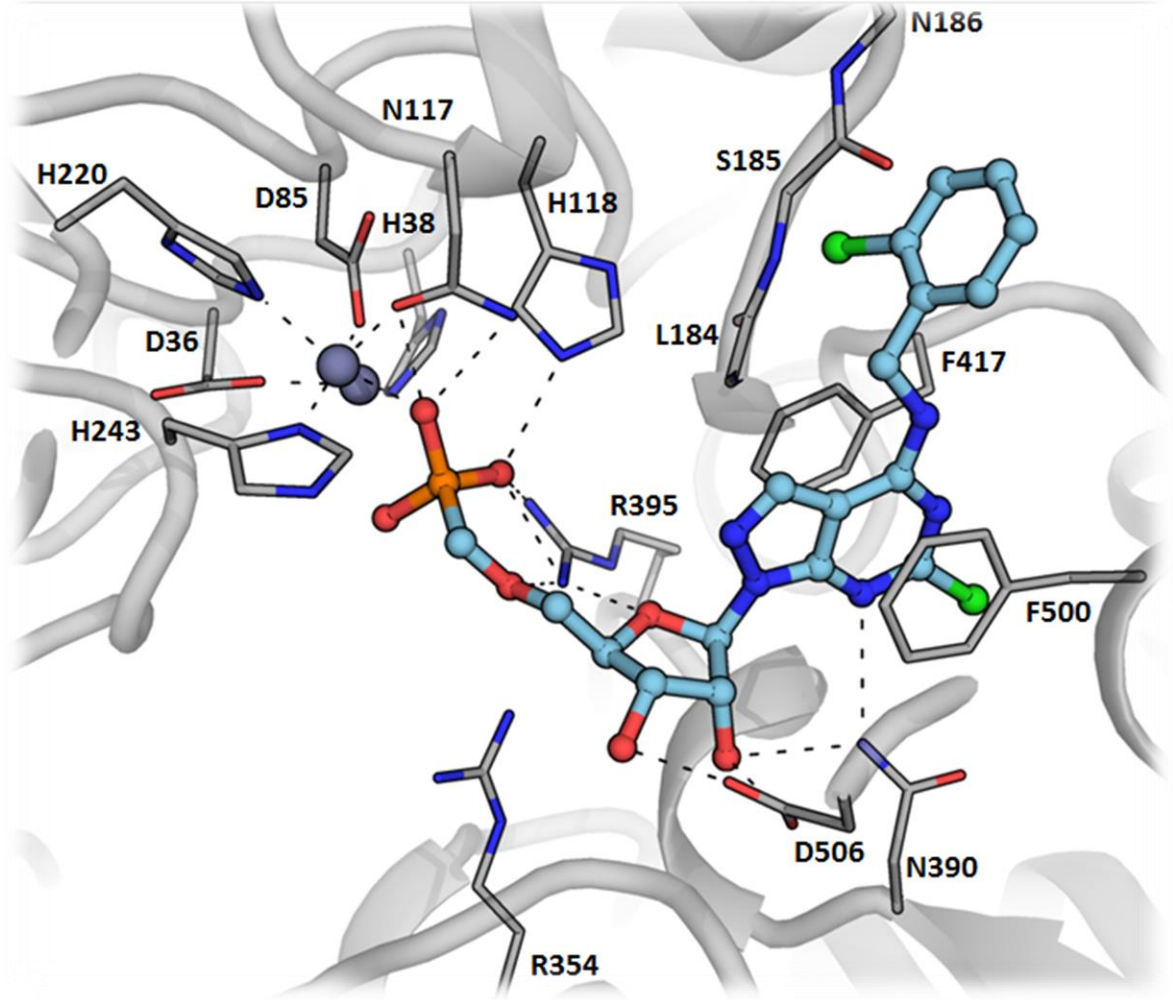


5

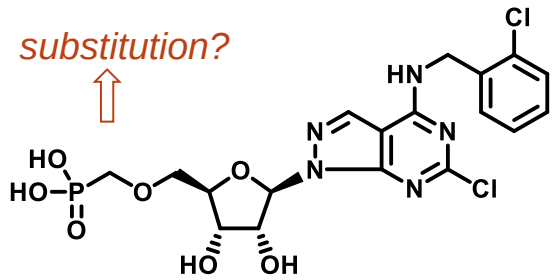
Biochem IC_{50} : **29** nM
Rat PO C_{max} : **0.11** µM
Rat PO AUC_{inf} : **0.66** µM*hr

- **Replace bisphosphonate motif to reduce overall polar surface area and charge**
- **Internal-capped phosphonate tolerated; linker length to *exo* phosphonate important**
- **Ether-linked phosphonic acid shows early signs of oral bioavailability**

Co-crystal structure of **5** with CD73 provided possible directions for potency improvement



substitution?



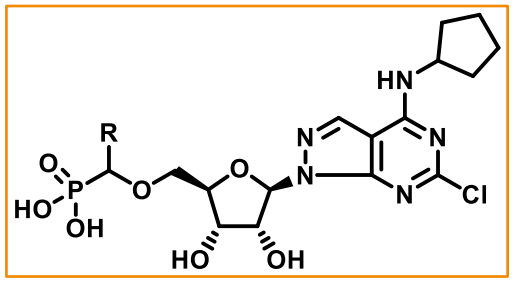
5: IC_{50} = 29 nM

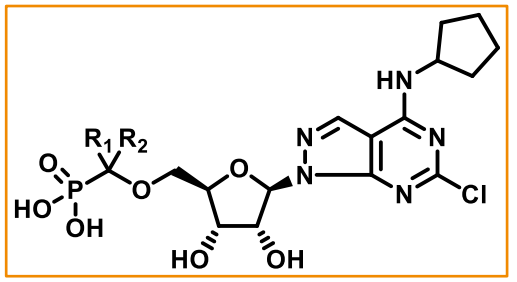
- **Can α-substitution further improve potency?**

α-Substitution identified key functional groups to increase potency

Compound	6	7	8	9	10	11	12	13	14
CD73 IC_{50} (nM)	11	18	2.4	0.96	28	559	108	193	387

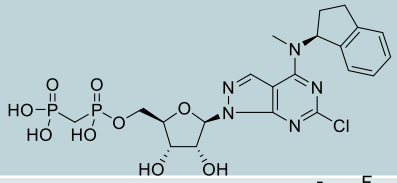
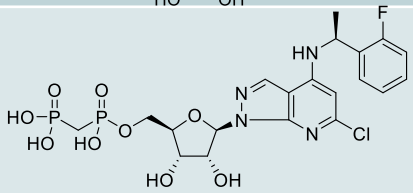
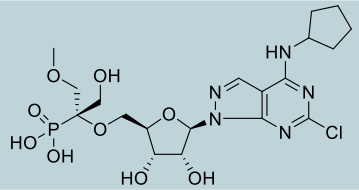
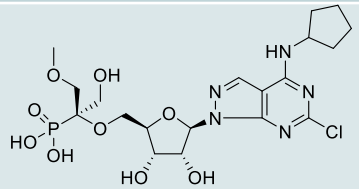
Compound	15	16	17	18	19	20	21	22
CD73 IC_{50} (nM)	1.3	>5000	97	10	23	31	0.57	0.53

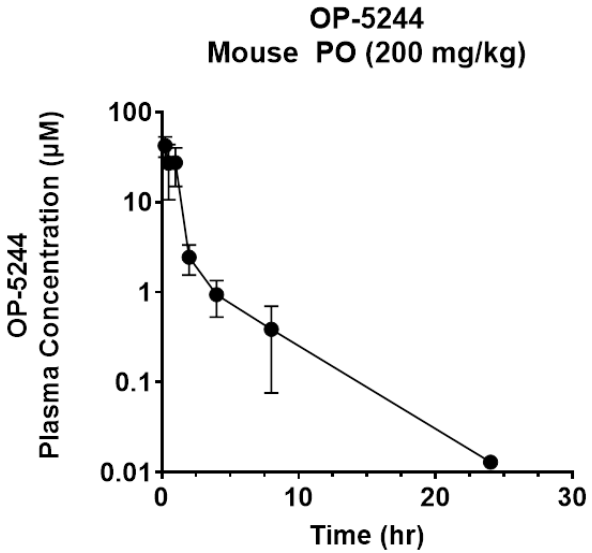




- **The oxygen in CH_2OR possibly interacts with CD73**
- **Disubstituted analogs 21 and 22 are more potent than mono-substituted 8 and 9**

Discovery of potent and orally bioavailable CD73 Inhibitor **OP-5244**

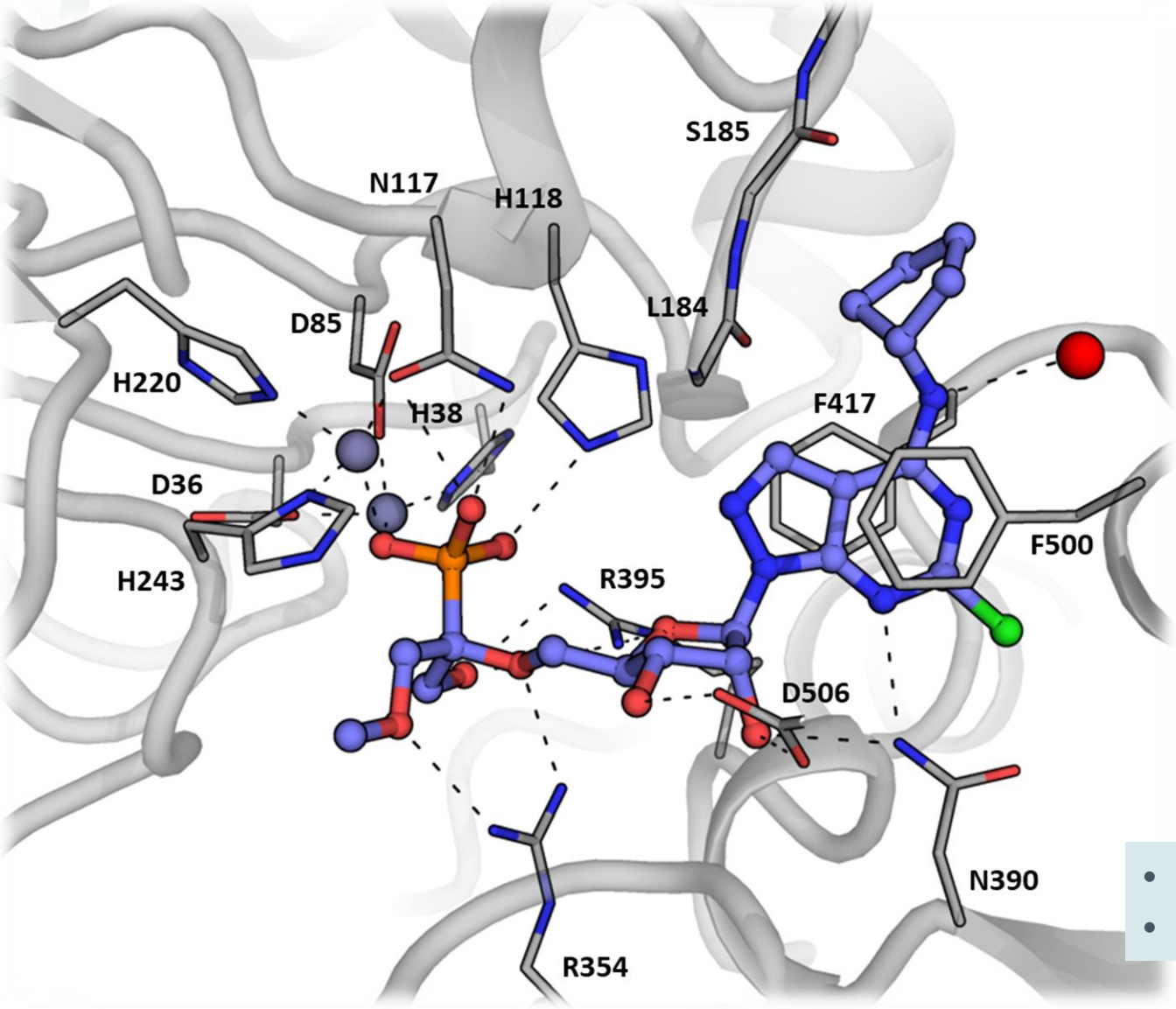
Compound	Structure	Biochem	H1568	EMT6	Mouse PO (200mg/kg)		
		IC_{50} (nM)	EC_{50} (nM)	EC_{50} (nM)	AUC_{inf} (μM*h)	C_{max} (μM)	$t_{1/2}$ (hr)
1		0.52	-	-	no oral exposure		
AB680*		0.86	3.3	198	Clinical trial (IV formulation)		
23 OP-5244		0.25	0.79	14	45.1	42.2	3.3
24		1.0	10.4	-	-		

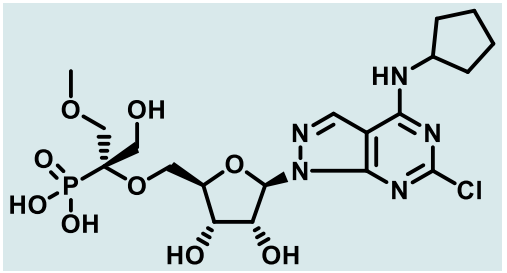


- **OP-5244 has comparable potency to bisphosphonic acid series**
- **OP-5244 shows good oral bioavailability in mouse**

*Bowman C.E. *et al*, Biochemistry 2019, 58, 3331-3334.

Co-crystal structures confirmed key interactions for potency improvement of **OP-5244**

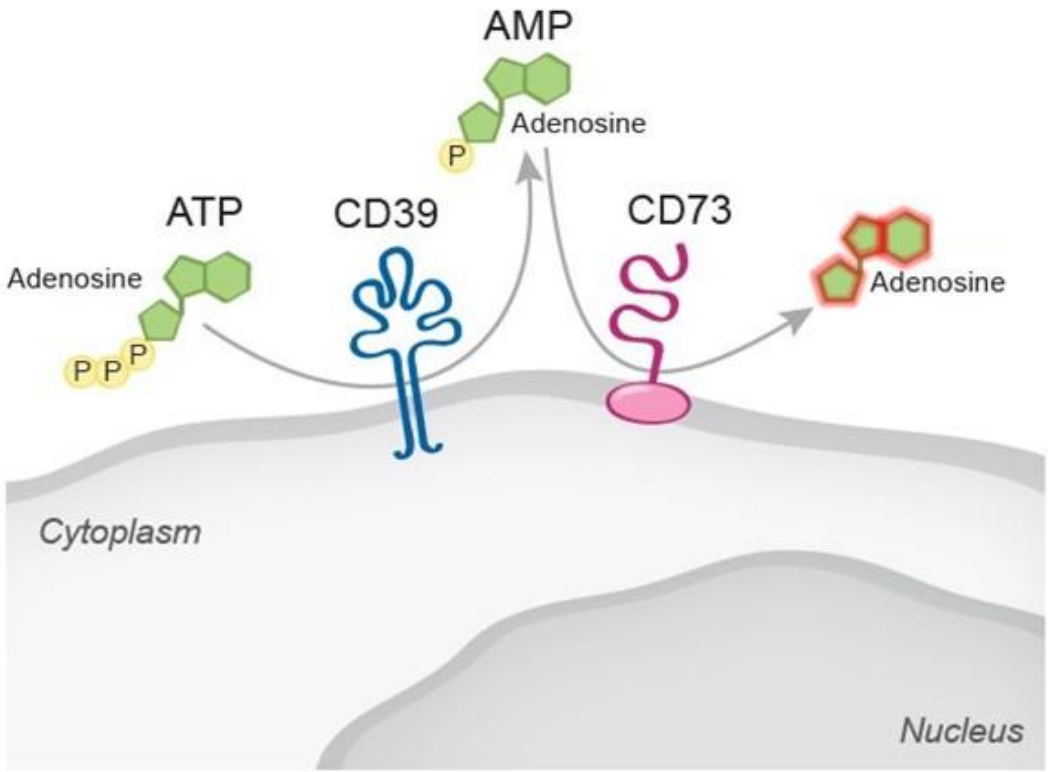


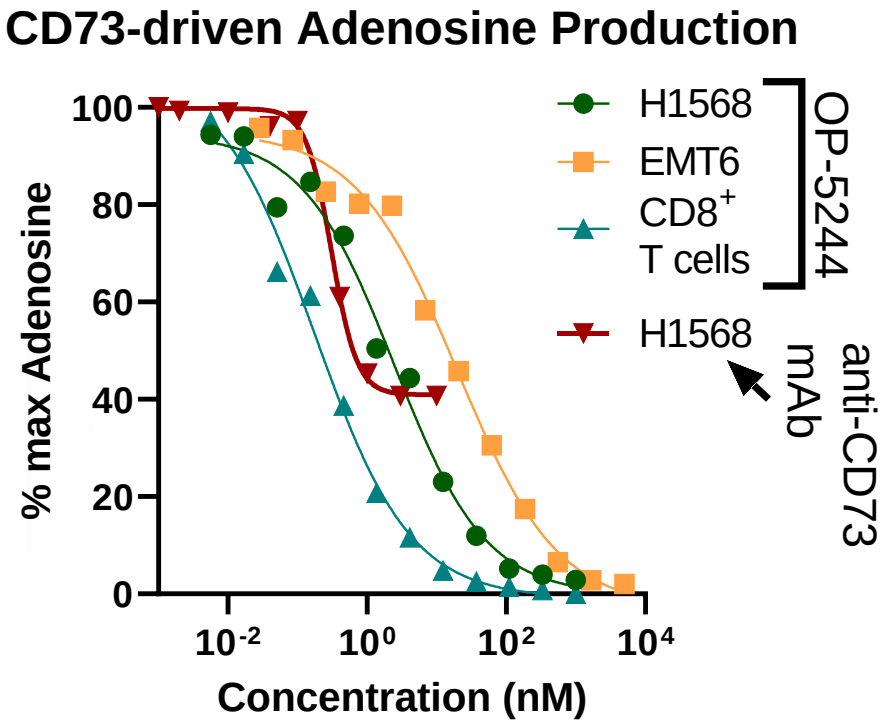


OP-5244: IC_{50} = 0.25 nM

- **CH_2OH/CH_2OMe H-bonds with Arg 354/395**
- **Replaced the phosphonate H-bond interactions**

OP-5244 fully suppresses ADO Production

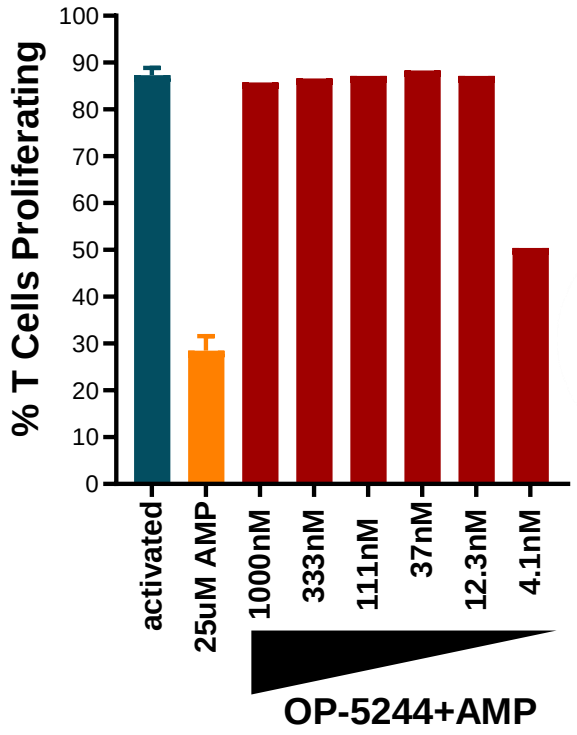




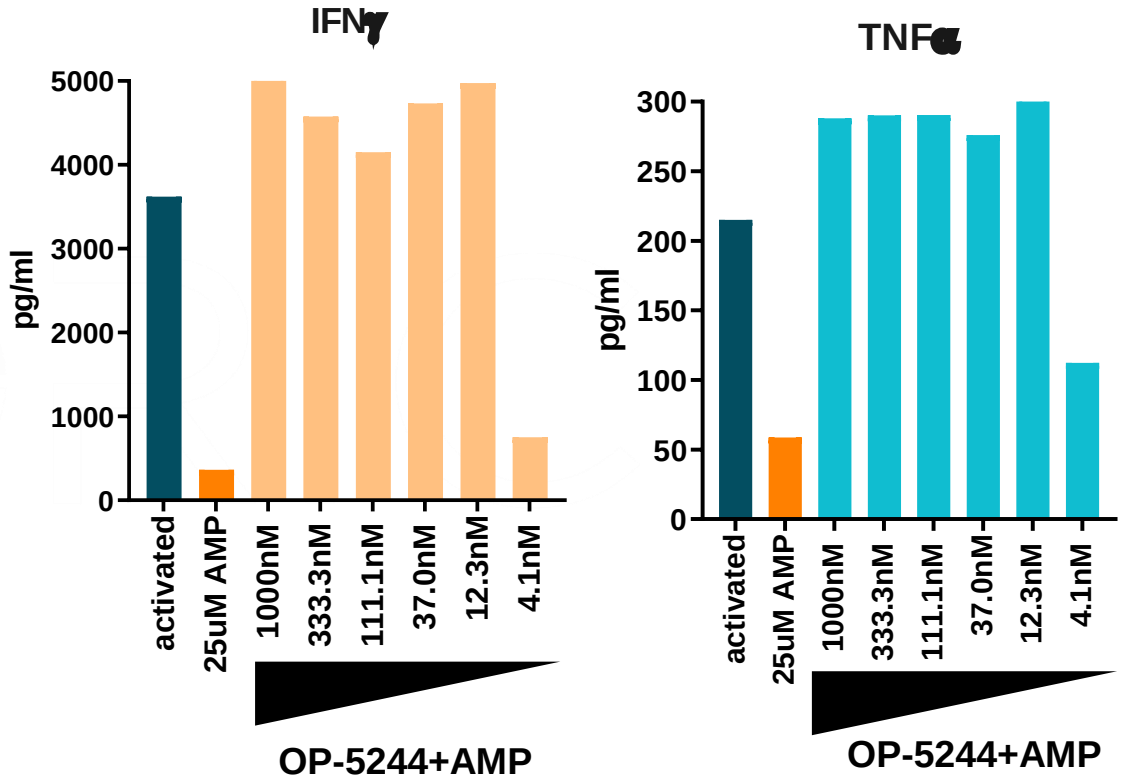
- **OP-5244 inhibited ADO production from AMP in tumor cells & $CD8^+$ T Cell (EC_{50} = 0.22 nM)**
- **A CD73-targeted antibody incompletely inhibits AMP conversion to ADO**

OP-5244 rescues immunosuppressive effects of AMP on T cells

T cell proliferation



Cytokines

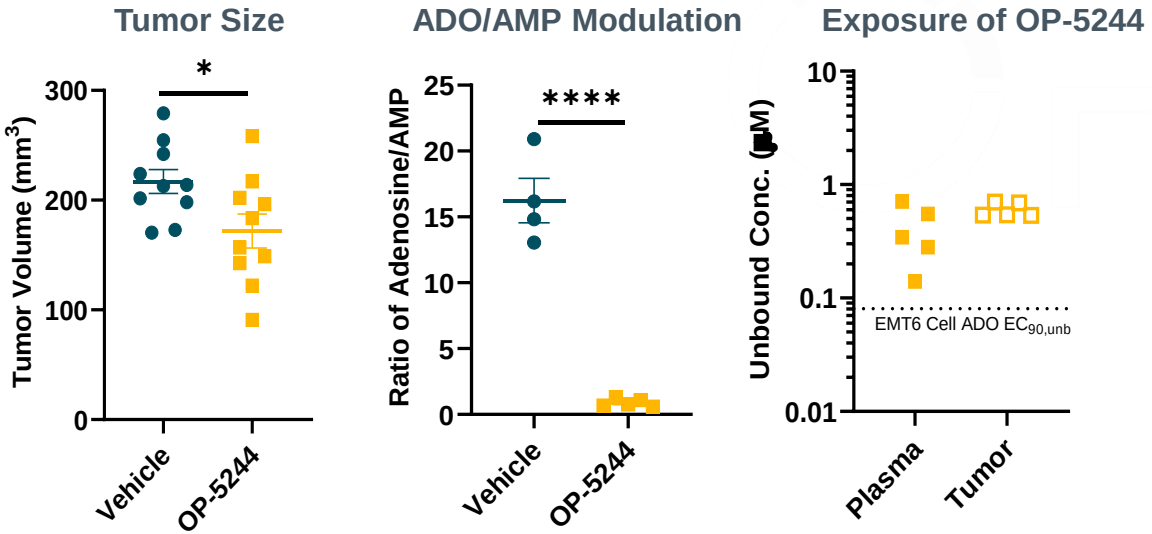


OP-5244 rescued CD8⁺ T cell proliferation and cytokine (IFNγ and TNFα) production in the presence of AMP

OP-5244 reduces tumor size, ADO/AMP ratio and reverses immunosuppression *in vivo*

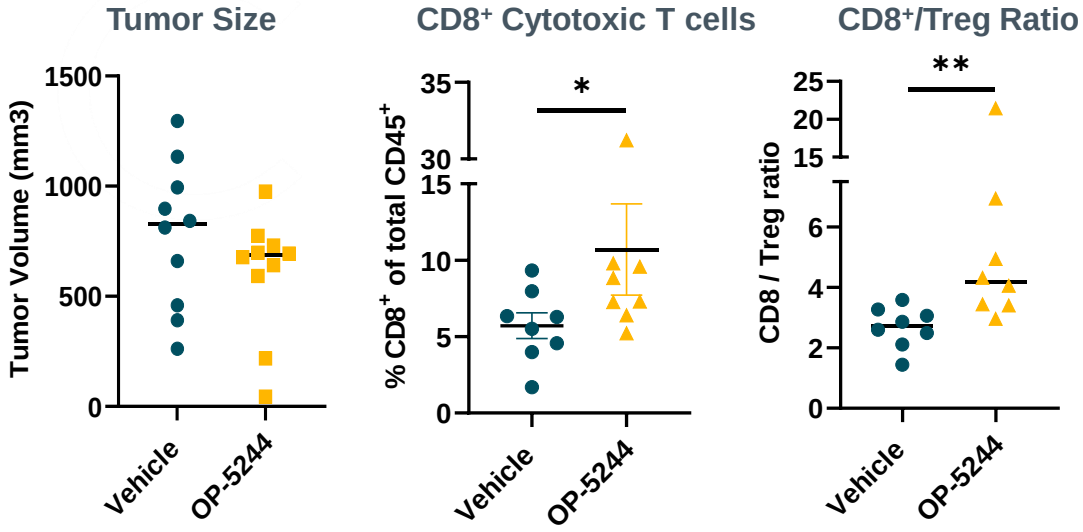
- OP-5244 exhibits anti-tumor effects as a single agent
- OP-5244 modulates intra-tumoral adenosine pathway
- OP-5244 activates tumor-mediated immune response

EMT-6 Murine Breast Cancer Model in BALB/c Mice



- OP-5244: 15 mg/kg/day mini pump infusion
- Tumor measurement on Day 13
- Tumor adenosine, exposure measurement on Day 13
- *, p<0.05: ****, p<0.0001 by t-test

E.G7-OVA Murine T Cell Lymphoma Model in C57BL6 Mice

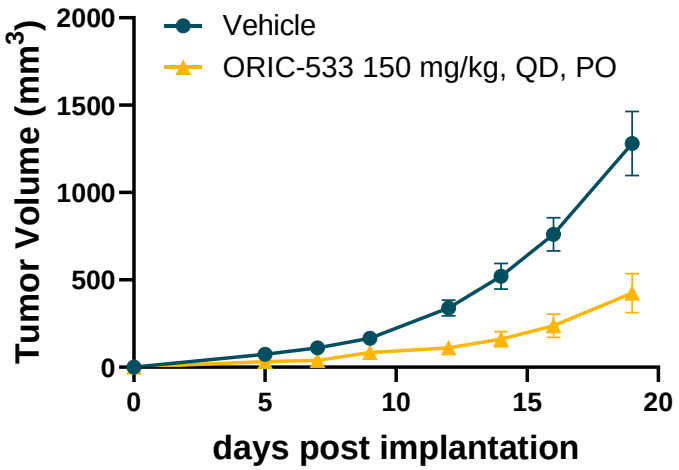


- OP-5244: 150 mg/kg, BID x 16, PO
- Tumor measurement on Day 15
- TIL analysis on Day 16
- *, p<0.05: **, p<0.01 by t-test

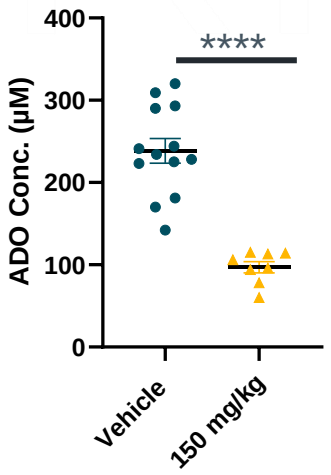
Upcoming AACR presentations featuring ORIC-533 development candidate

- **Poster #10268:** An orally bioavailable inhibitor of CD73 reverts intratumoral immunosuppression and promotes anti-tumor responses
  - Significant single agent anti-tumor activity of ORIC-533 associates with reversed immunosuppression
- **Poster #4317:** CD73 inhibition with a novel orally bioavailable small molecule blocks adenosine production and rescues T-cells activation in high AMP conditions

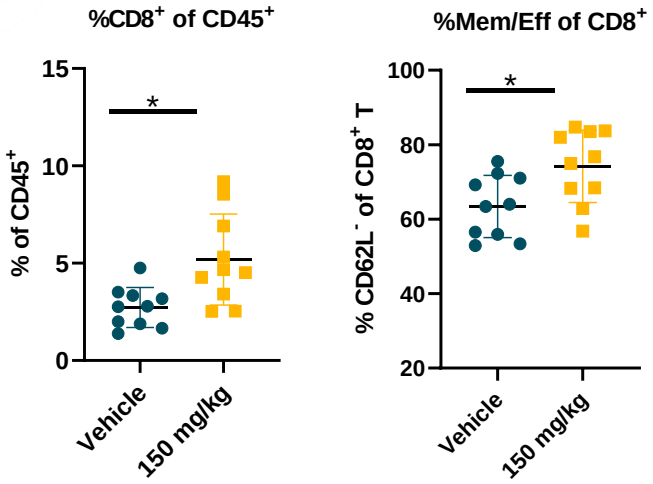
Tumor Growth Inhibition



Tumor Adenosine



Tumor T Cell Modulation



Conclusions

- Designed novel orally bioavailable mono-phosphonic acid CD73 inhibitors
- Ether phosphonic acids with α,α-disubstitution gained additional interactions with CD73 and further potency enhancement
  - equipotent relative to the bisphosphonic acid series
- Small molecule CD73 inhibitor represents a potential therapeutic approach to reverse immunosuppression within the tumor microenvironment
  - **OP-5244** fully rescues T cell proliferation and cytokine production from ADO-mediated suppression *in vitro*
  - **OP-5244** reduces tumor size, modulates intra-tumoral ADO pathway and reverses immunosuppression *in vivo*
  - **OP-5244** is a prototype for further optimization/clinical candidate identification

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Qiuping Ye

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