

# Targeting Innate Immunity

## Ectonucleotide Pyrophosphatase / Phosphodiesterase 1 (ENPP1)



**STINGRAY**  
THERAPEUTICS

# BEST IN CLASS INNATE IMMUNITY PROGRAM

## **ENPP1 inhibition: Upregulates innate immune response in tumors**

### **Activating innate immune response may improve immunotherapy responses**

- Previous intra-tumoral STING agonism (Aduro and Merck Phase 1-2)
  - Shows Pharmacodynamic (PD) effects in injected tumor (proof of principle)
  - Failed to produce a robust abscopal (ripple) effect
- Direct systemic STING agonism may cause auto-immunity (lupus, Aicardi-Goutières)

### **ENPP1 inhibition is superior to targeting STING directly**

- ENPP1 is primed by DNA damage and cytoplasmic DNA leaks (safer, specific)
- Broader immune repertoire: Targets both Innate (STING) and Adaptive (Adenosine)
- ENPP1 is a player in DNA damage response and chemo-resistance

### **SR-8541A is a small molecule with**

- Excellent preclinical efficacy and oral bioavailability
- Safe and tolerable
  - Knockout animals are viable
  - ENPP1 germline mutations in humans are viable
  - Preliminary rodent tolerability is safe

# “PIPELINE IN A TARGET”

## ENPP1 INHIBITORS HAVE A LARGE POTENTIAL IN:

### Infectious Diseases

- Mycobacterial diseases: CDNP is a “bacterial ENPP1” that promotes virulence by inhibiting cGAS-STING-IFN signaling pathway.
  - Stingray has compounds that hit CDNP and ENPP1
  - For mycobacterium avium (MAC) and mycobacterium tuberculosis
- Hepatitis B and other DNA viruses
  - STING Pathway is vital in the host response to clear HBV
- Covid-19 dramatically suppresses interferon response

### Auto-antibody Diseases

- Hemophilia, Anti-Factor VIII antibody disease
- Lupus Nephritis
  - Long lived plasma cells rely on ENPP1

# OUTSTANDING BIOTECH SPECIALISTS, FROM DISCOVERY THROUGH PHASE 2



We are based in Texas, because Texas has grant support for oncology companies.



**Jon Northrup**  
CEO & Co-Founder



**Sunil Sharma, MD FACP**  
Chief Med. Officer & Co-Founder



**Mohan Kaadige, PhD**  
Head, Biology



**Monil Shah, PharmD, MBA**  
VP, Development



**Srinivas Kasibhatla, PhD**  
Chemistry



**Alexis Weston**  
Manager BD, Biology



**Scott Jordan**  
Chief Business Officer



**Uma Bhatt, CPA**  
Chief Accounting Officer





# SCIENCE AND DEVELOPMENT

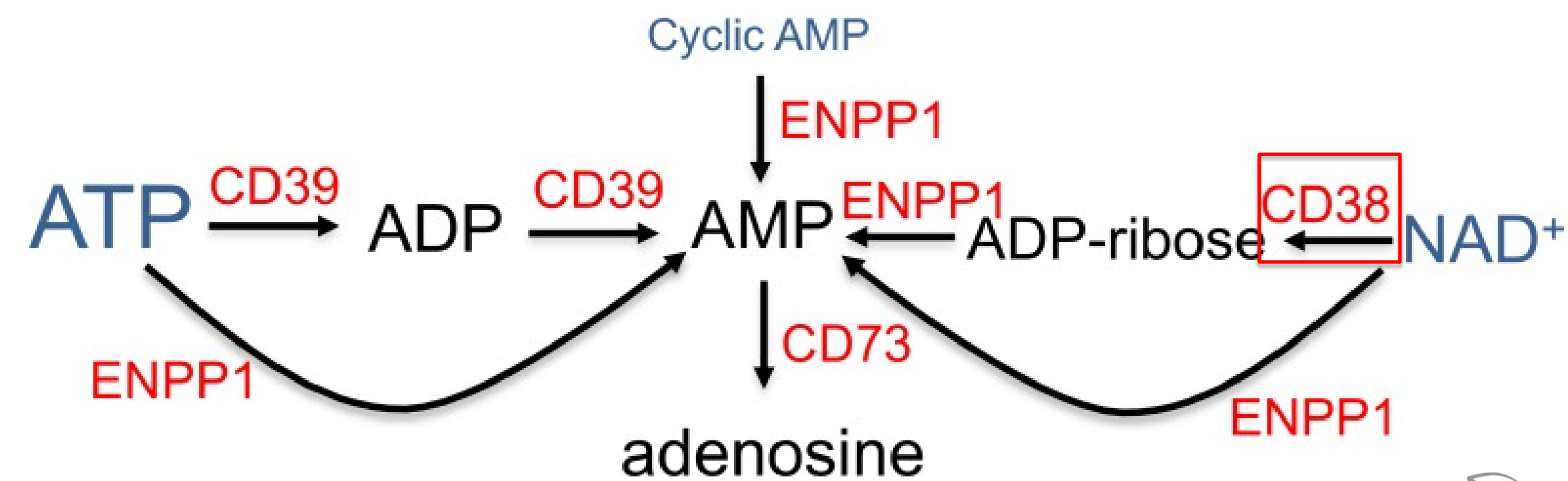
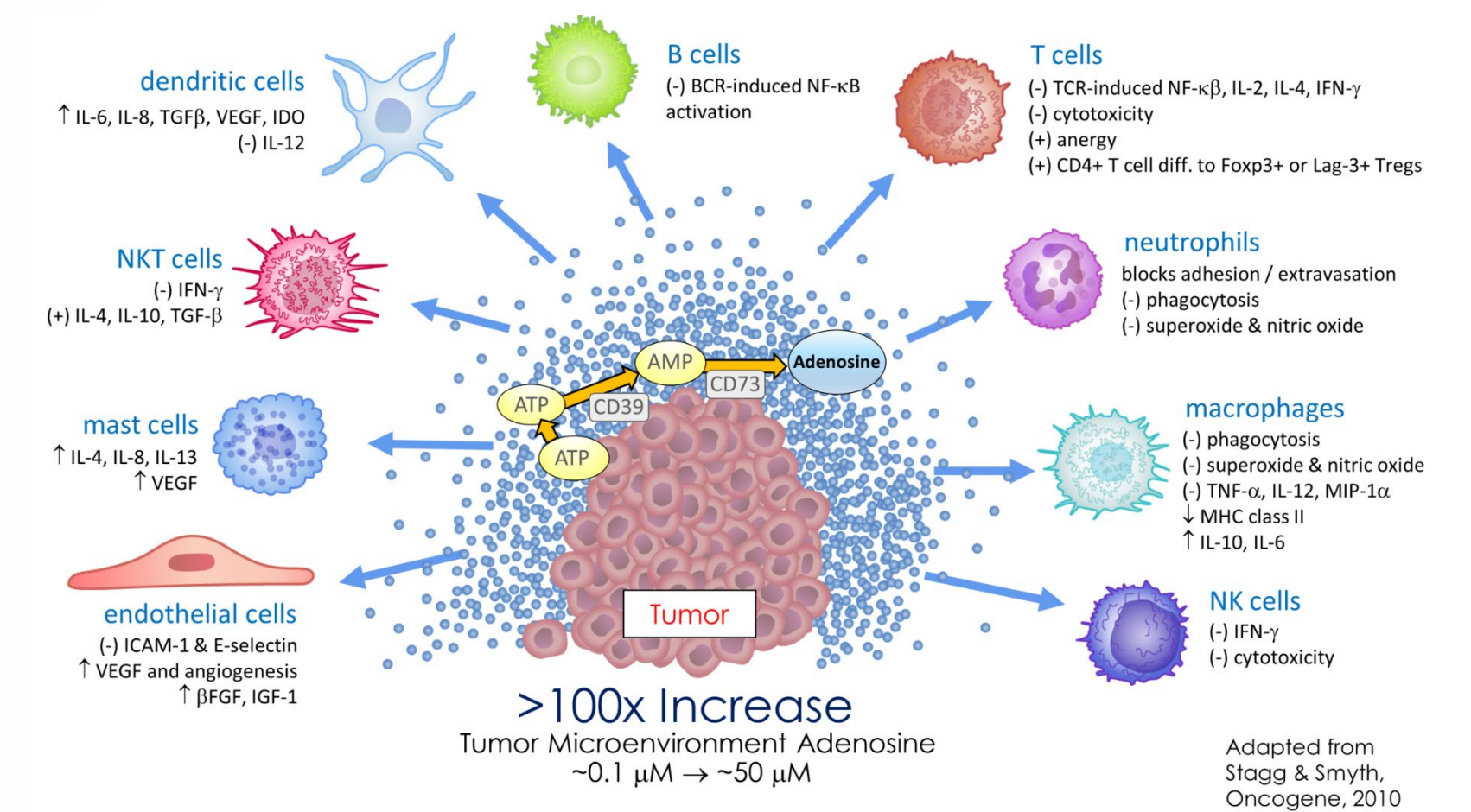
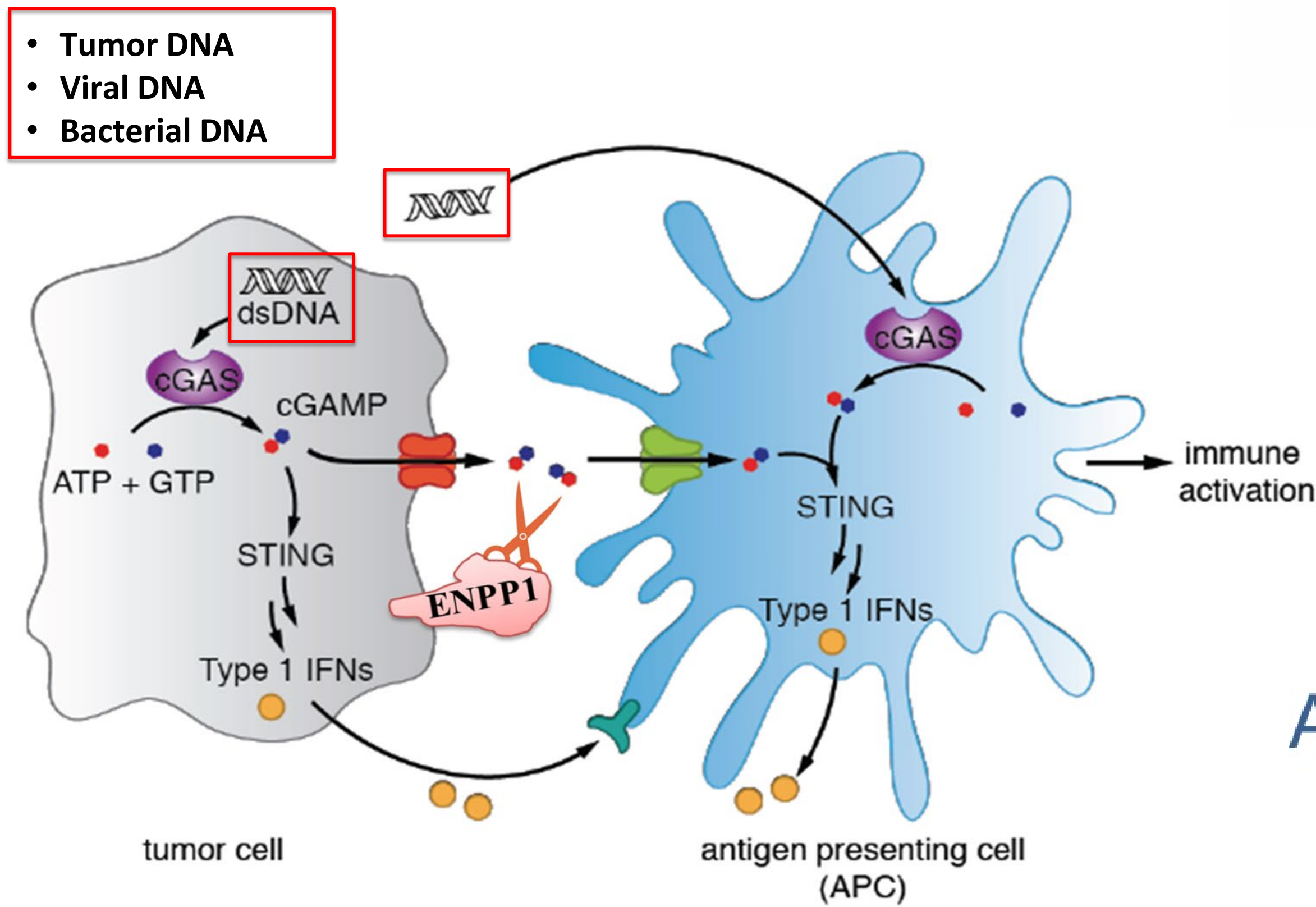


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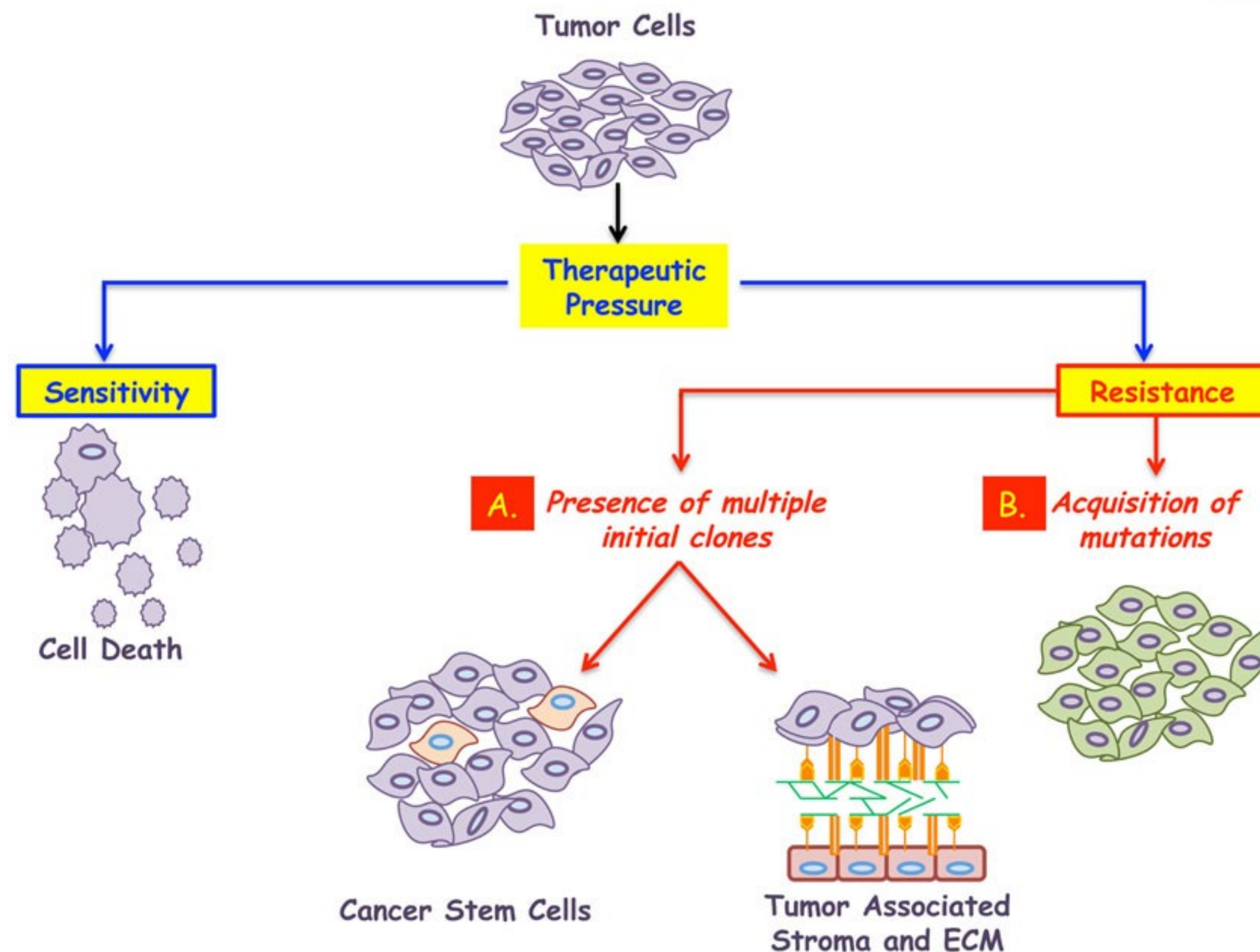
# RATIONALE FOR TARGETING ENPP1: INNATE AND ADAPTIVE IMMUNITY

Regulates STING-dependent innate immune response

Contributes to the production of adenosine, a key immune suppressive molecule in the TME



# INNATE IMMUNE RESPONSE IS TIED TO CHEMO RESISTANCE



## Survival & Relapse Through:

- Alterations of drug metabolism (increased efflux, decreased uptake, enhanced detoxification, sequestration)
- Modification of drug targets
- Dysregulation of apoptotic proteins
- Enhanced DNA repair
- Other routes

[Front Pharmacol.](#) 2013 Mar 14;4:28.

September 15, 2020

Proprietary

Stem cell characteristics in glioblastoma are maintained by the ENPP1

(Cell Death Differ. 2014 Jun;21(6):929-40)

Loss of microRNA-27b contributes to breast cancer stem cell generation by activating ENPP1

(Nat Commun. 2015 Jun 12;6:7318)

ENPP1 interacts with ABCG2 and promotes its surface localization

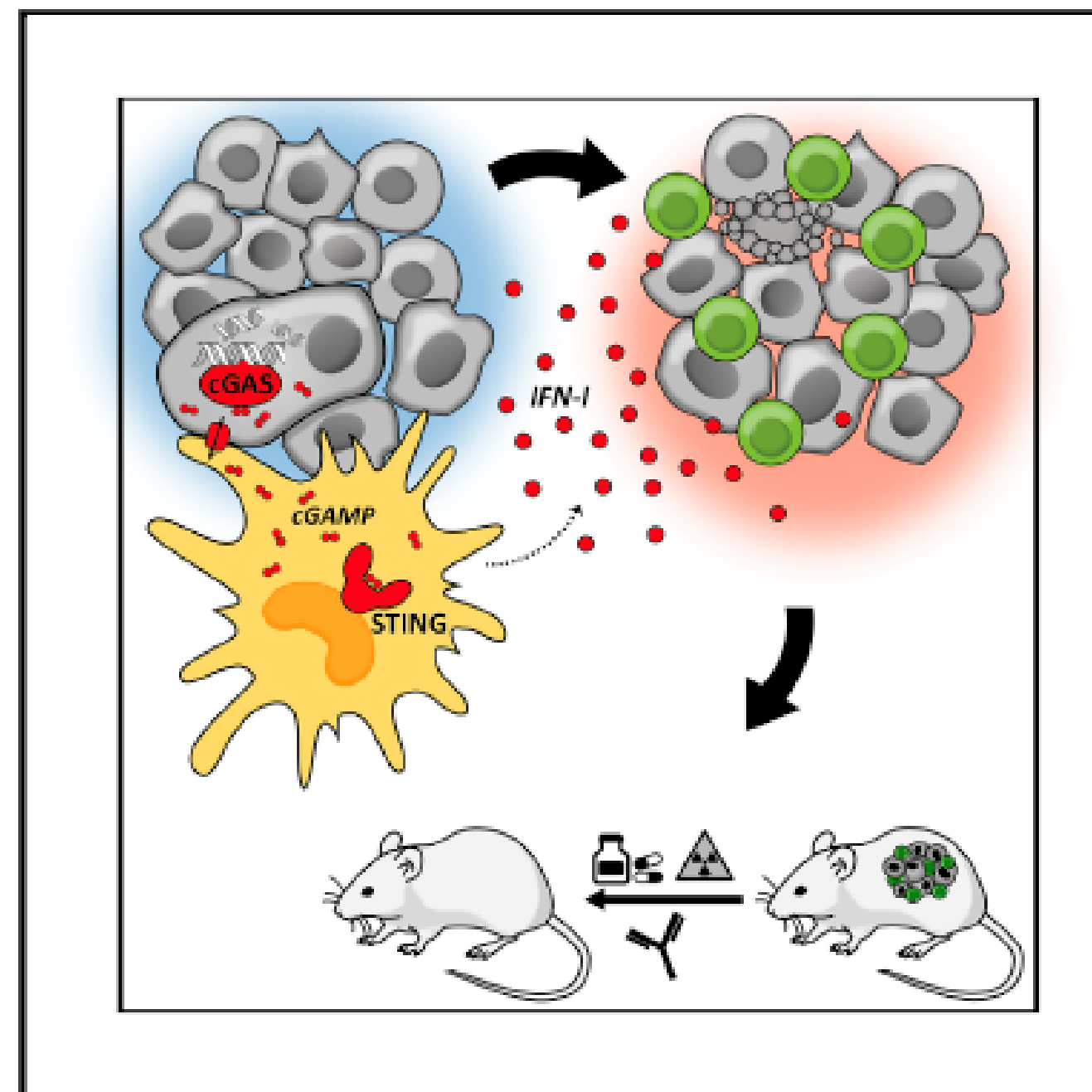
ENPP1 knockdown increases chemosensitivity

ENPP1 processes protein ADP-ribosylation in vitro

(FEBS J. 2016 Sep;283(18):3371-88)

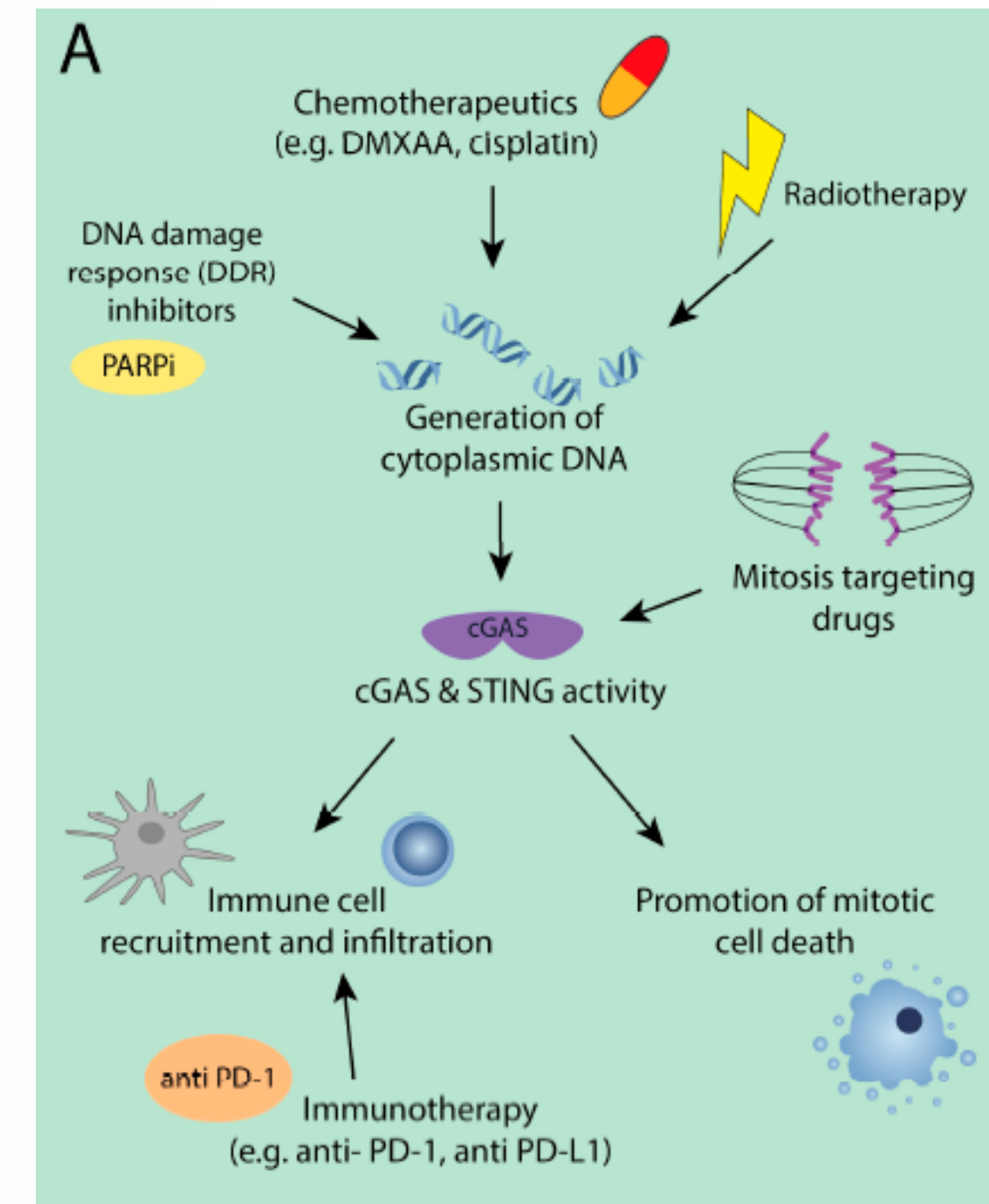
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# Cancer Cell Intrinsic cGAS Expression Mediates Tumor Immunogenicity



## Highlights

- cGAS in cancer and STING in host cells are minimal requirements to activate CD8<sup>+</sup> T cells
- Cancer cells transfer cGAMP to myeloid cells in the TME that make STING-dependent IFN-I
- Cancer-cell-intrinsic cGAS improves tumor immunogenicity and response to therapy



*Cells* 2019, 8, 1228; doi:10.3390/cells8101228



# LEAD AND BACK-UP SCAFFOLDS

## Scaffold 1

- Lead candidate: SR-8541A (5 nM)
- Selective

## Scaffold 2

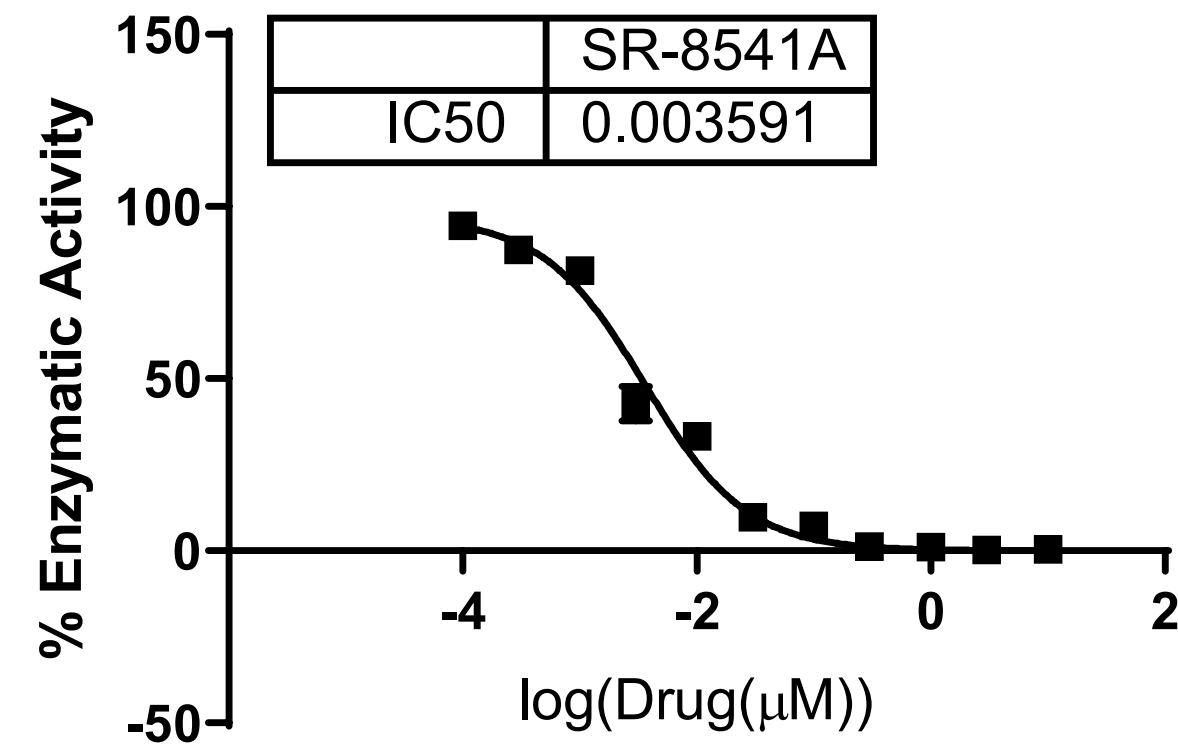
- SR-8542 (30 nM) and SR-8542-3 (6 nM)
- Selective

## Latest Patent covers 8500-8600 series compounds (clinical candidate) - Provisional

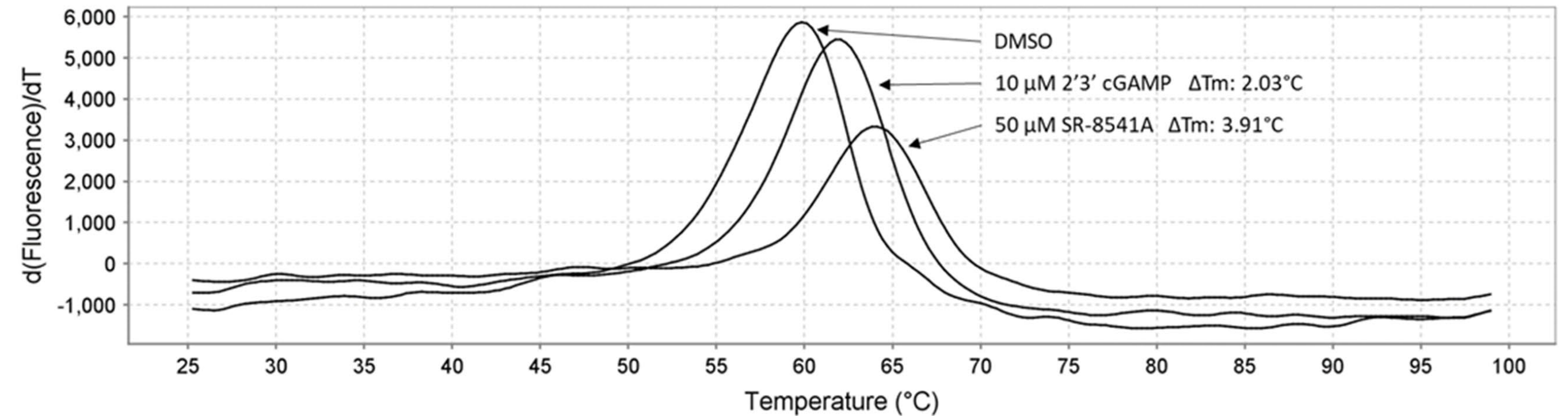
- Provisional filed February 5, 2020
- Fully owned by Stingray; no economic obligations

# SR-8541A IS A POTENT AND SELECTIVE INHIBITOR OF ENPP1

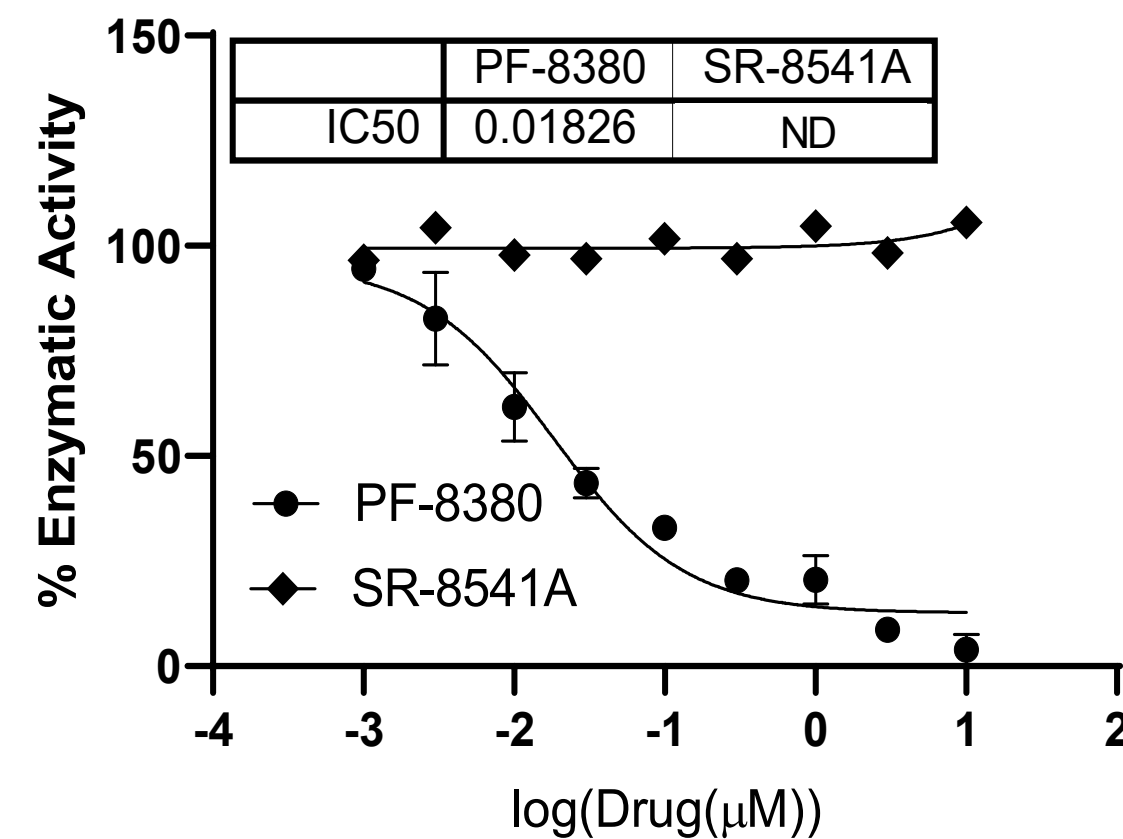
## ENPP1 enzymatic assay



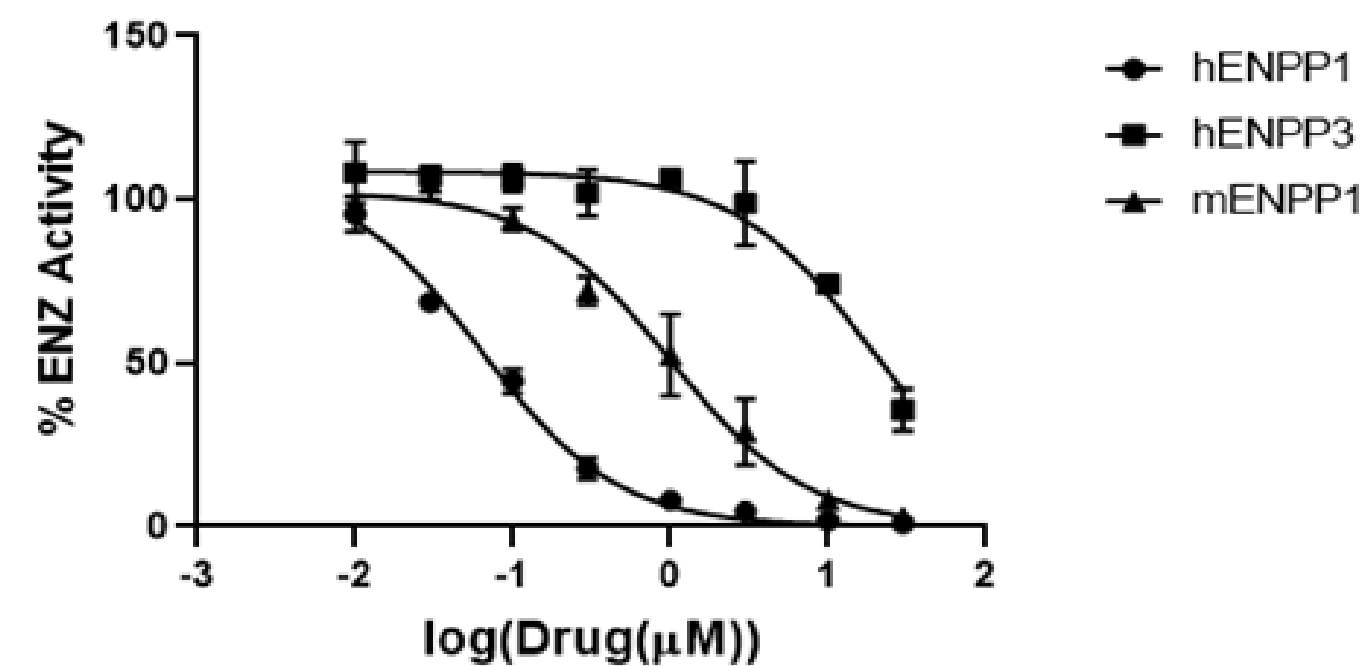
## ENPP1 Thermal Shift Assay (1 μg hENPP1/well)



## ENPP2 enzymatic assay



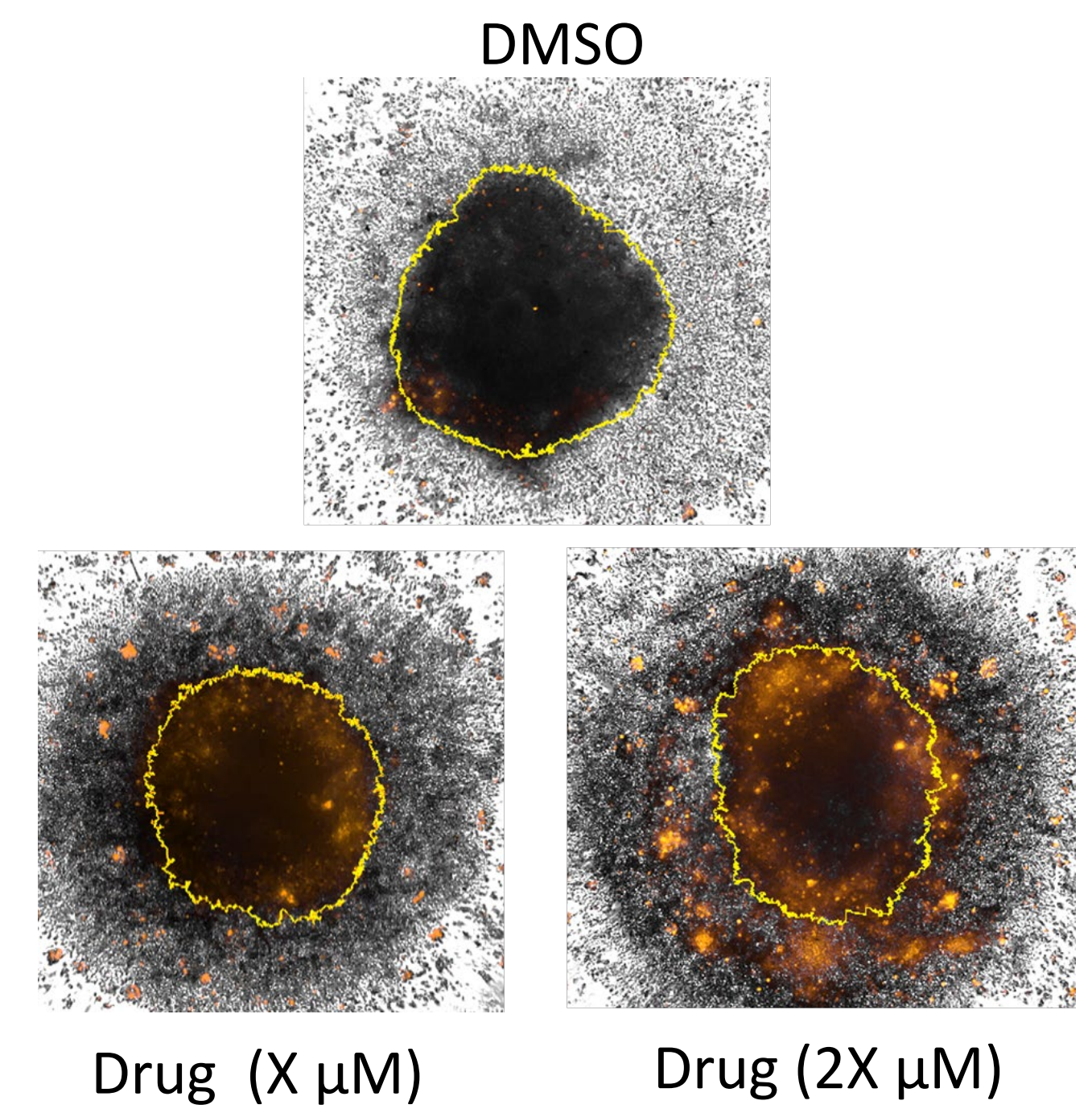
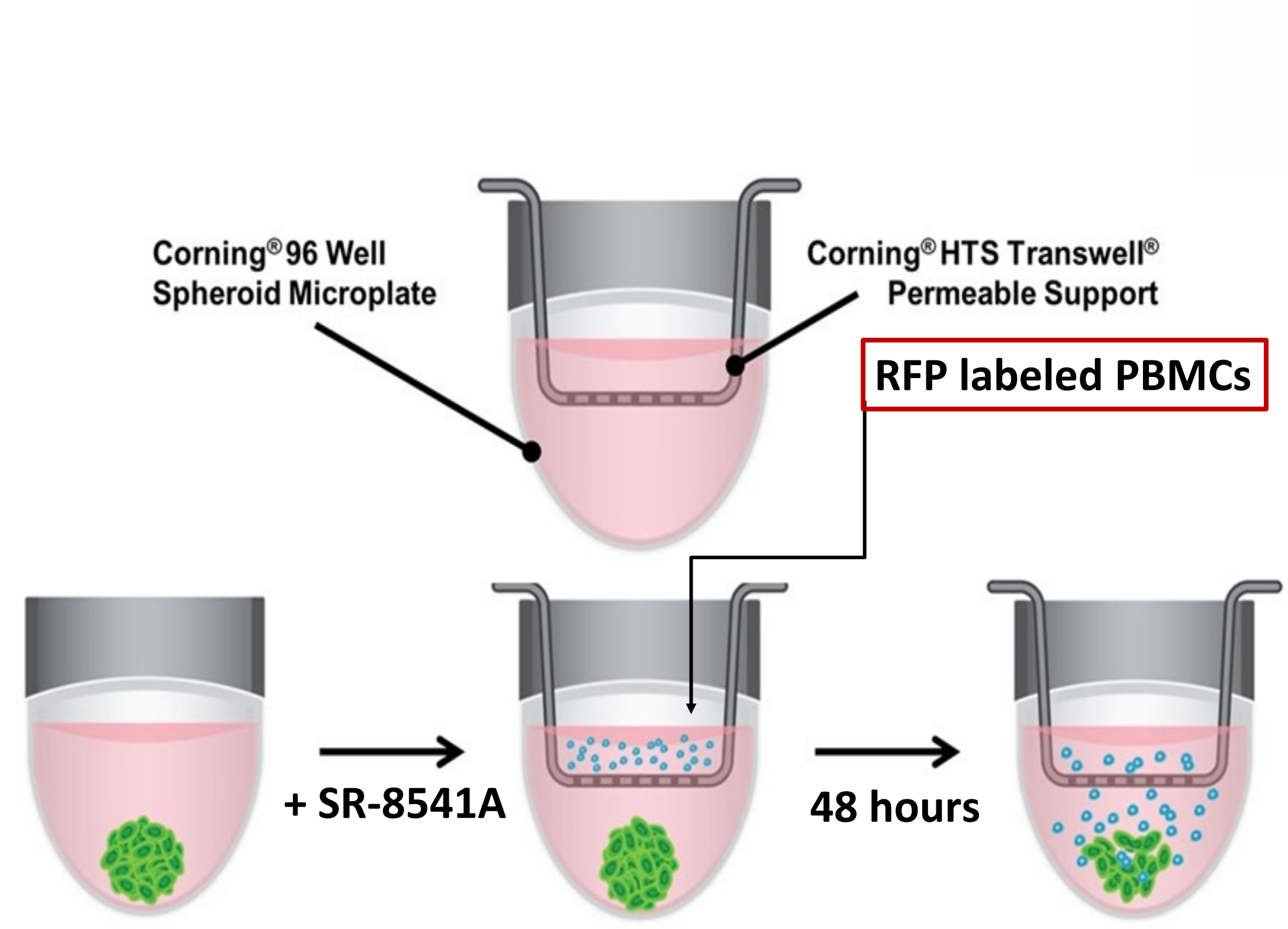
## Cell-based ENPP enzymatic assay



	hENPP1	hENPP3	mENPP1
IC50	0.06217	18.80	0.9865

- 0/6 hits in **p450 Enzyme panel** at 10 μM
- >10 μM against **hERG**
- 0/468 hits at 1 μM in **Kinome Panel**
- 0/13 hits in **PDE panel**
- 0/40 hits in **Bromodomain Panel**
- 0/168 hits the **GPCR Panel** at 10 μM

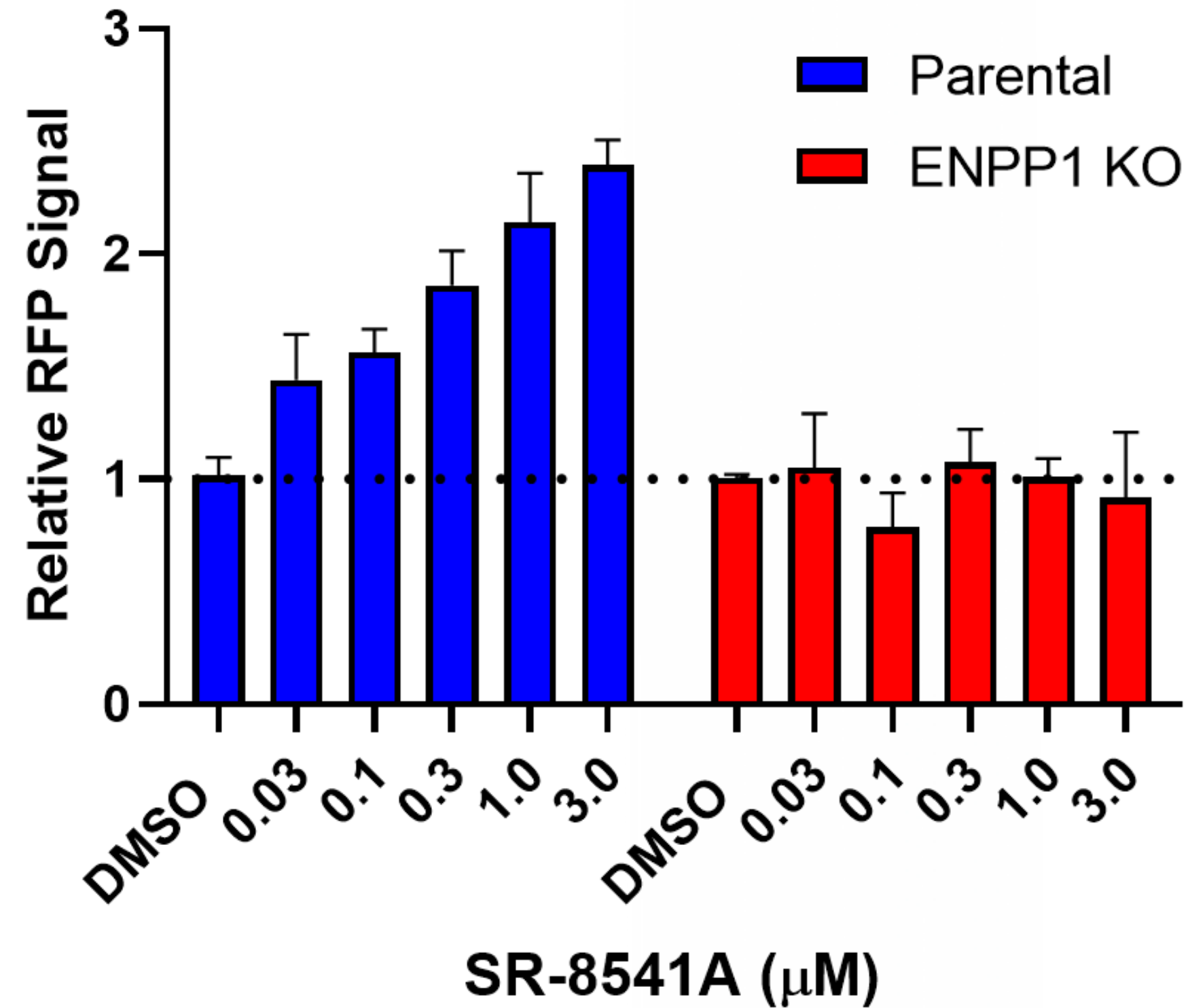
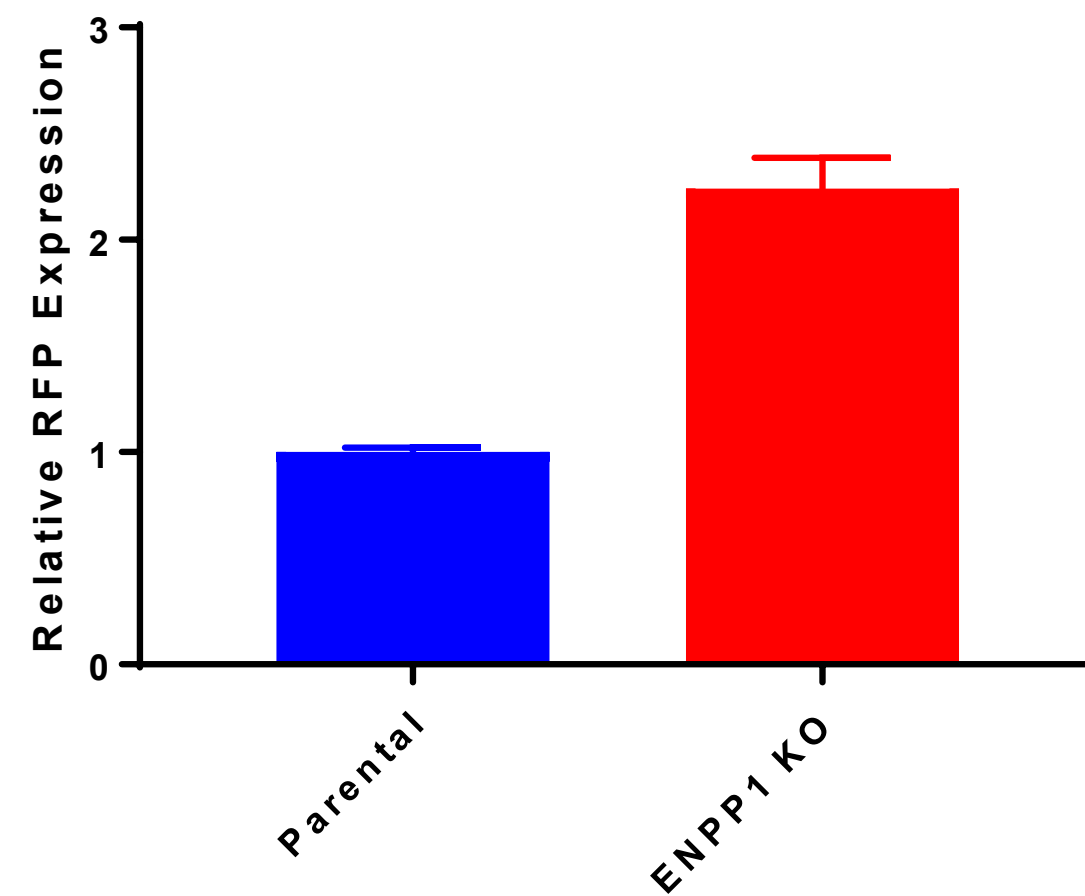
# IMMUNE INFILTRATION ASSAY



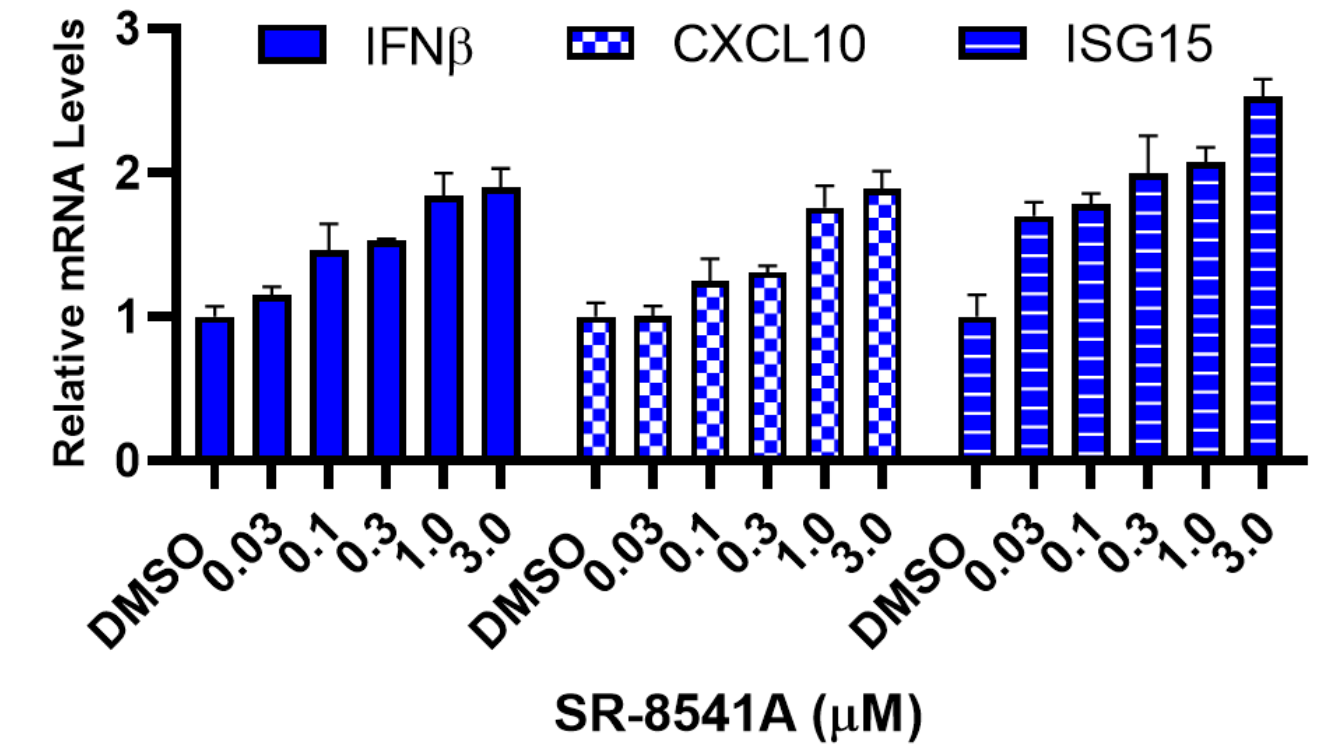
**Cytokines secreted in medium**  
**Gene expression changes in spheroid**  
**immune cell infiltration and tumor death**

# ENPP1 INHIBITORS ACTIVATE THE STING PATHWAY AND PROMOTE LYMPHOCYTE INFILTRATION IN BREAST CANCER

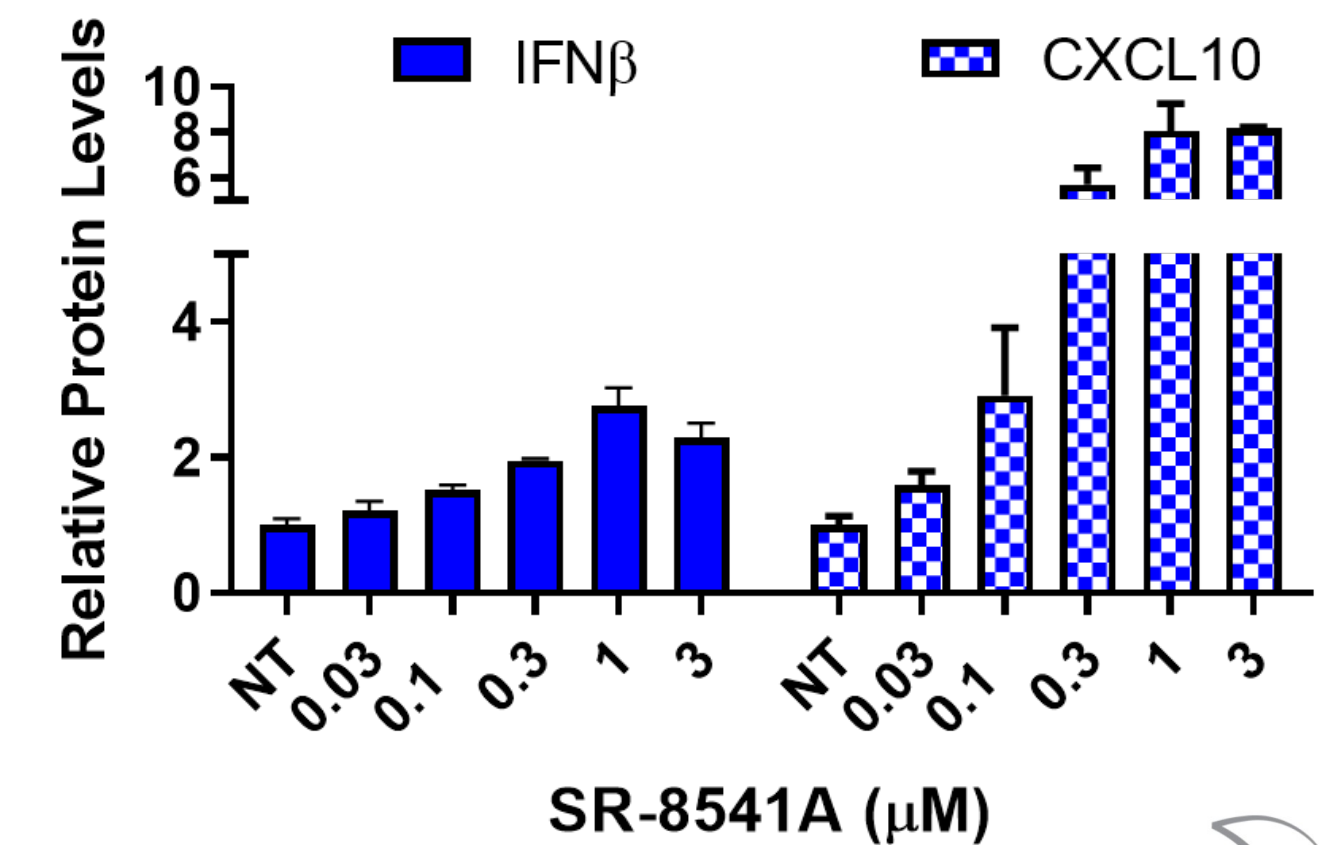
PBMC (RFP) Infiltration into Organoids  
MDA-MB-231 Cells



Gene Expression – RTPCR

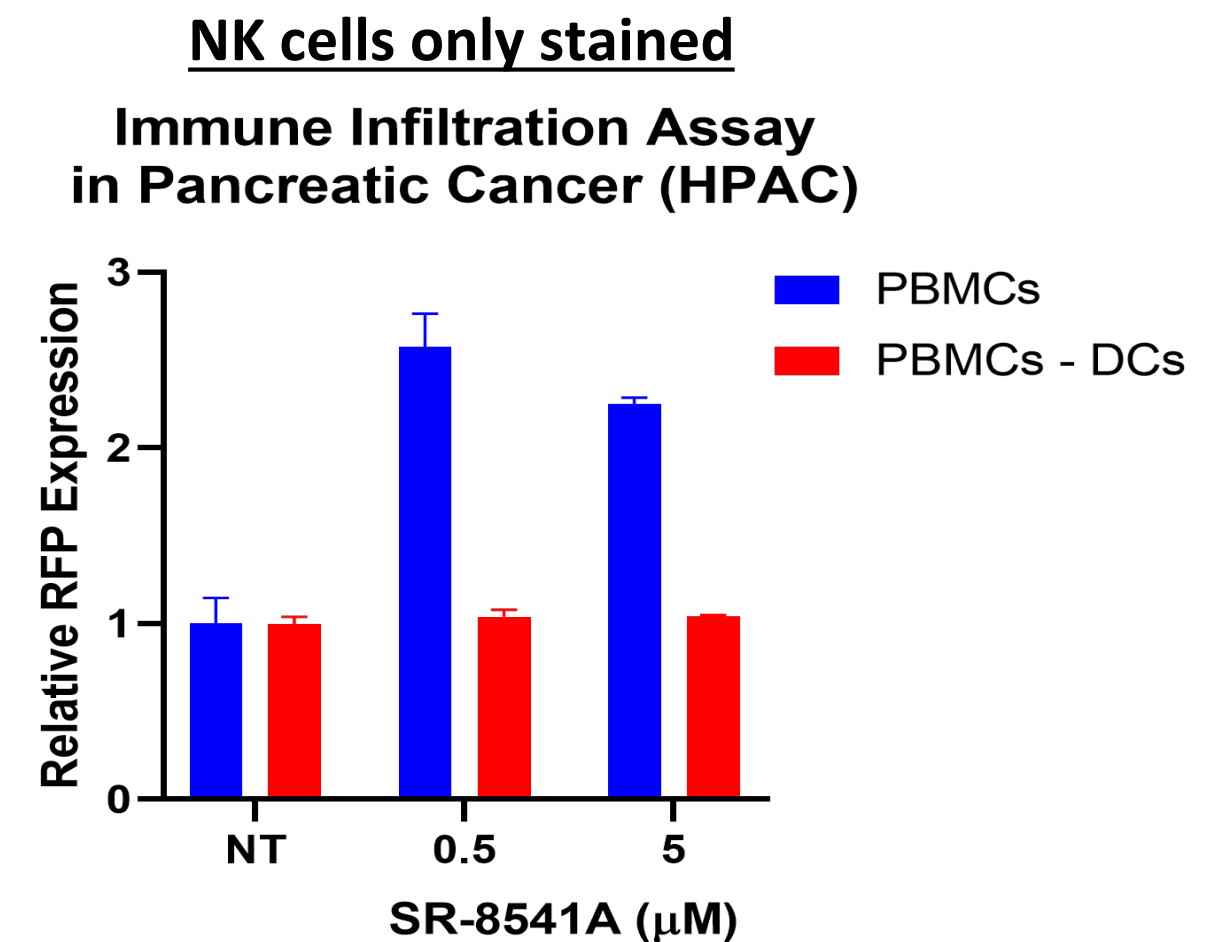
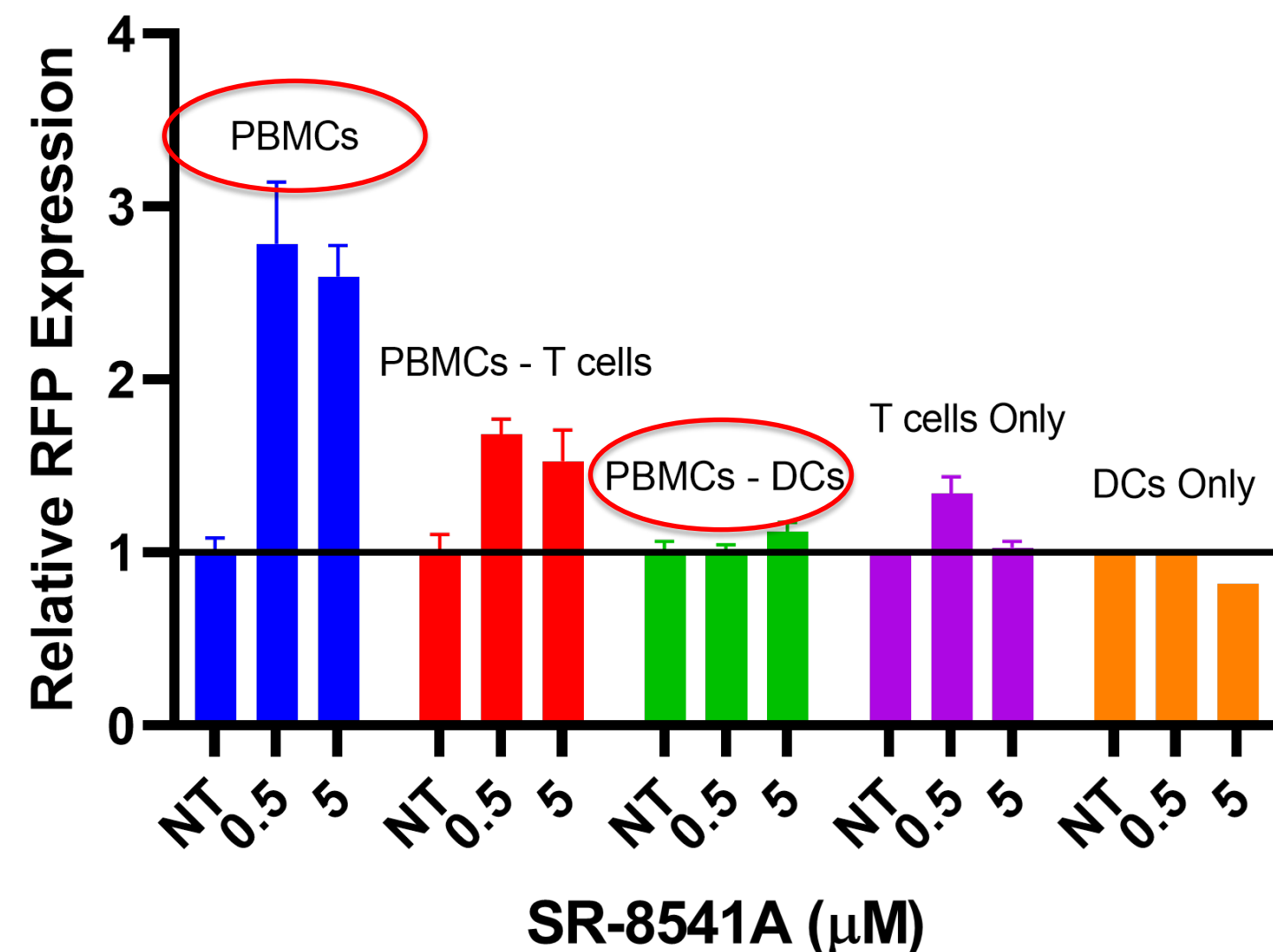
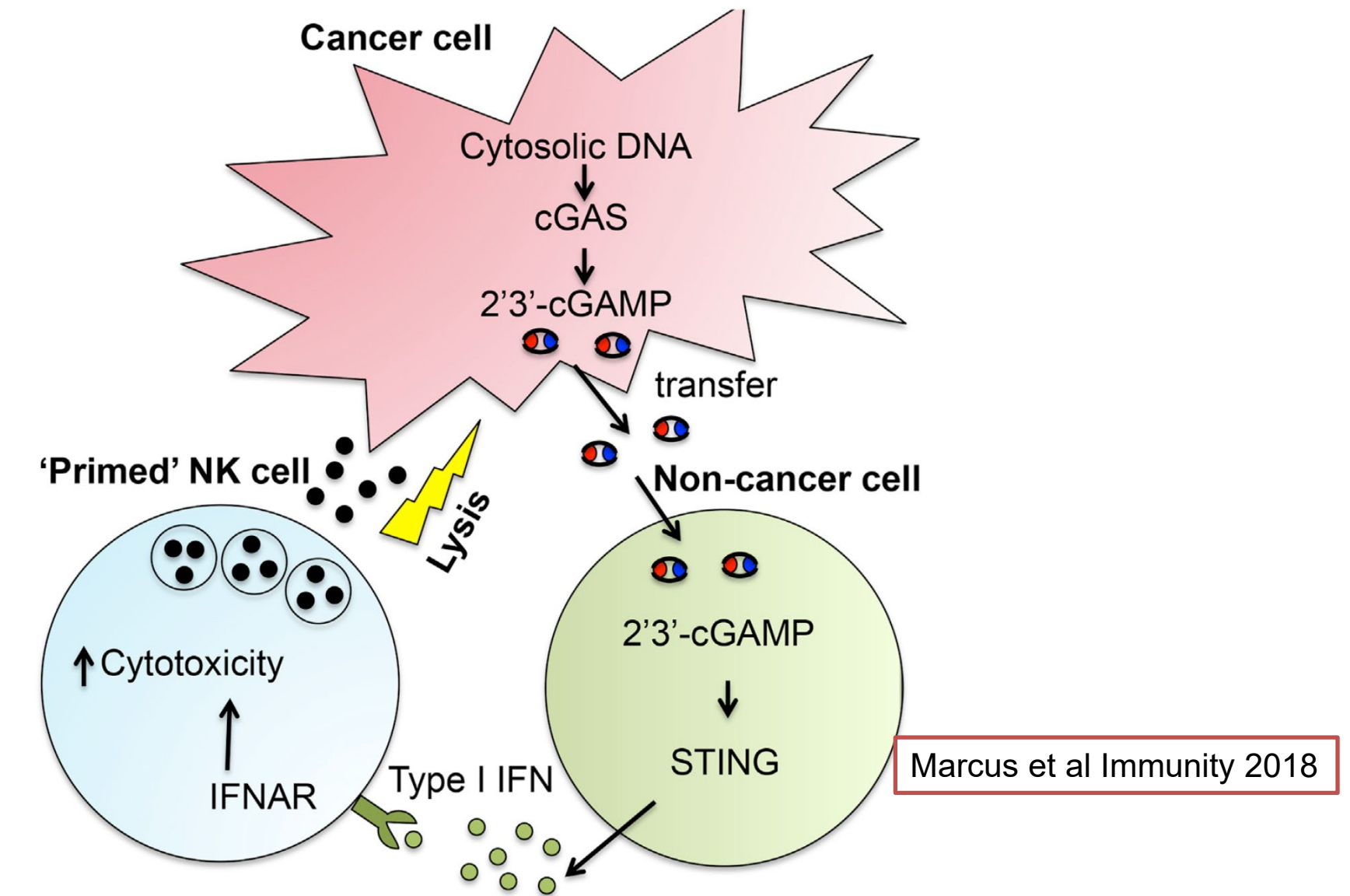


Protein Excretion – MSD

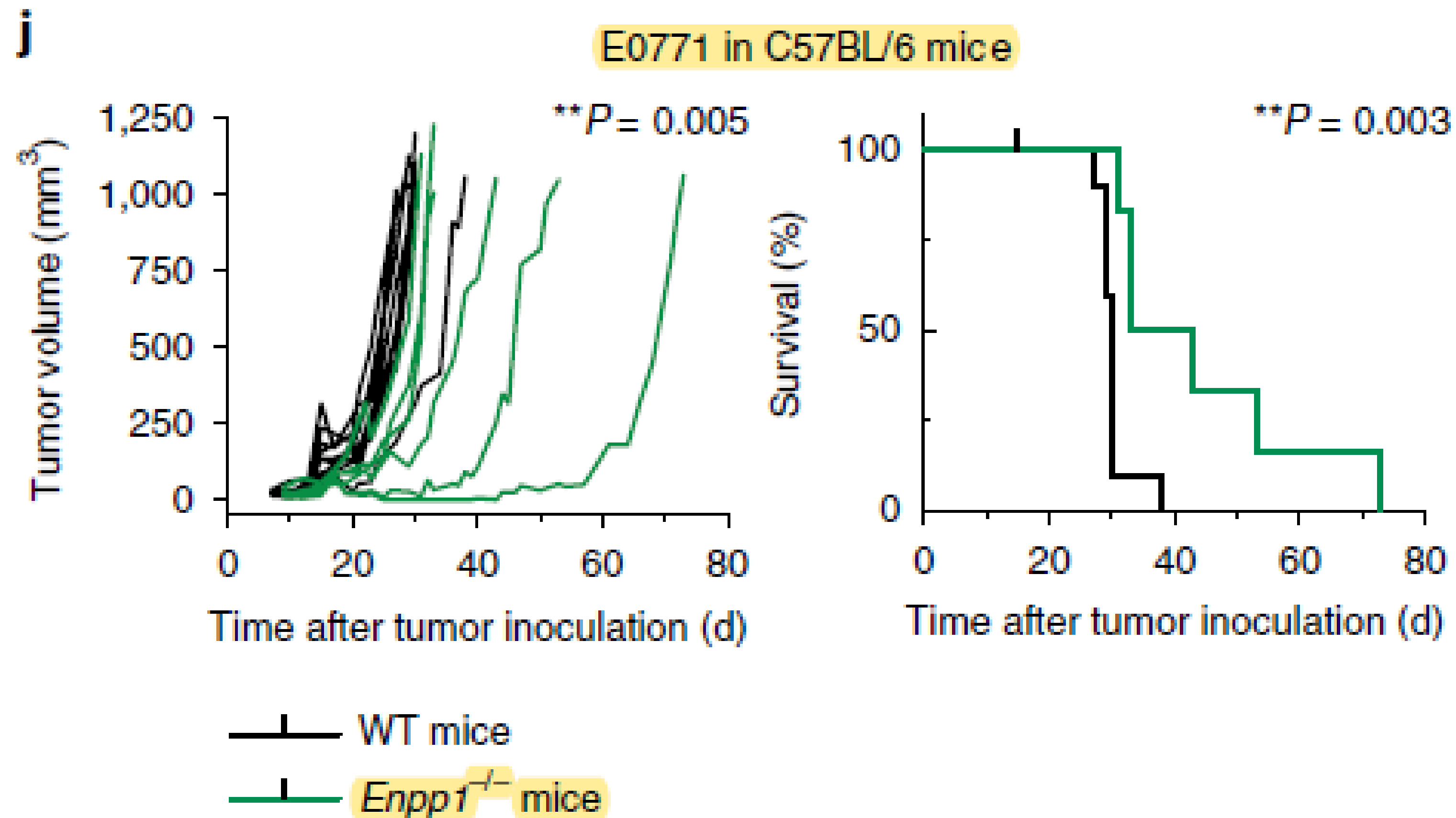


# WHICH CELLS ARE REQUIRED FOR INFILTRATION?

- Infiltration assay experiments clearly show:
  - Dendritic cells are essential
  - NK cells are primed and strongly participate in infiltration

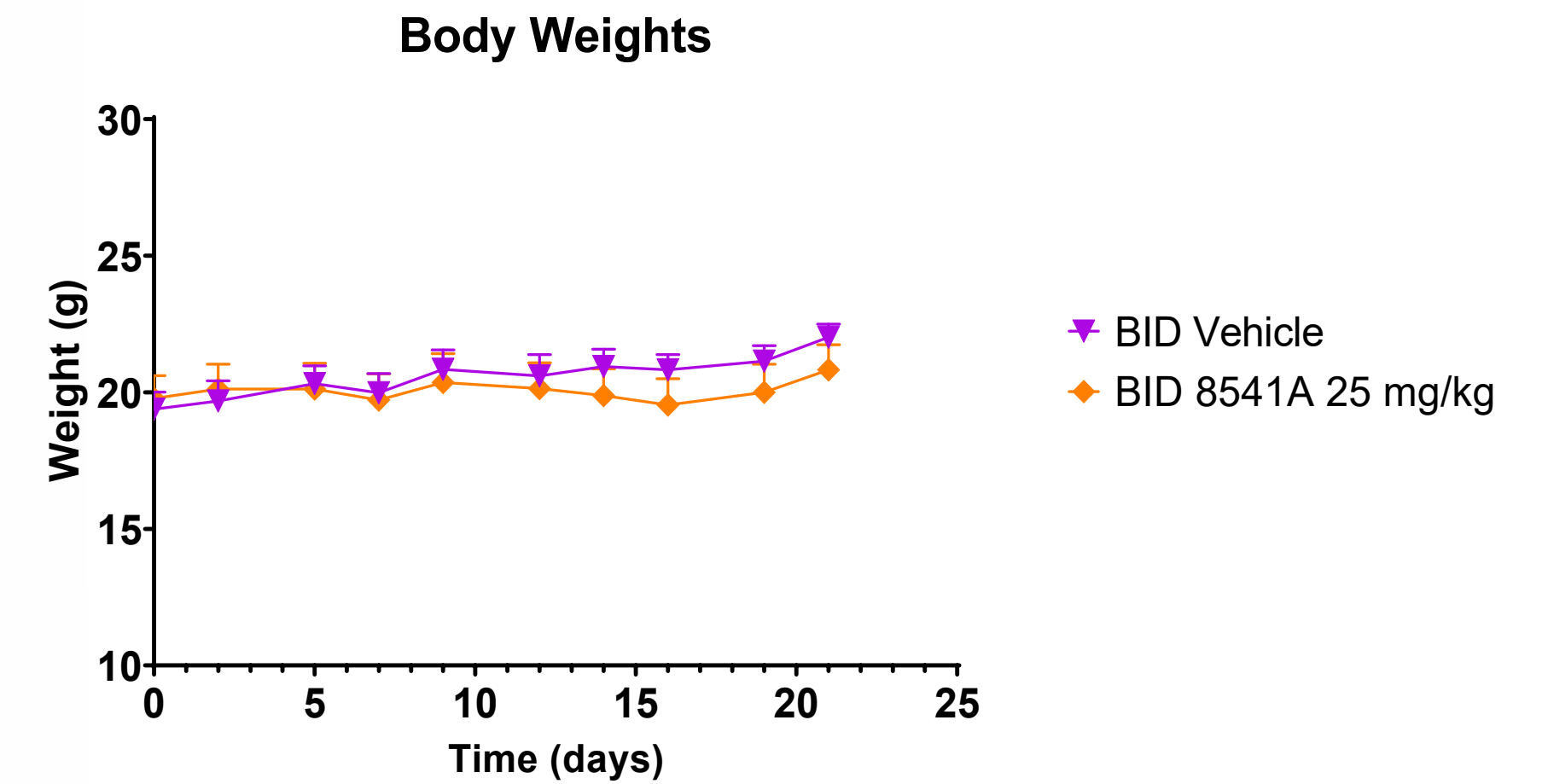
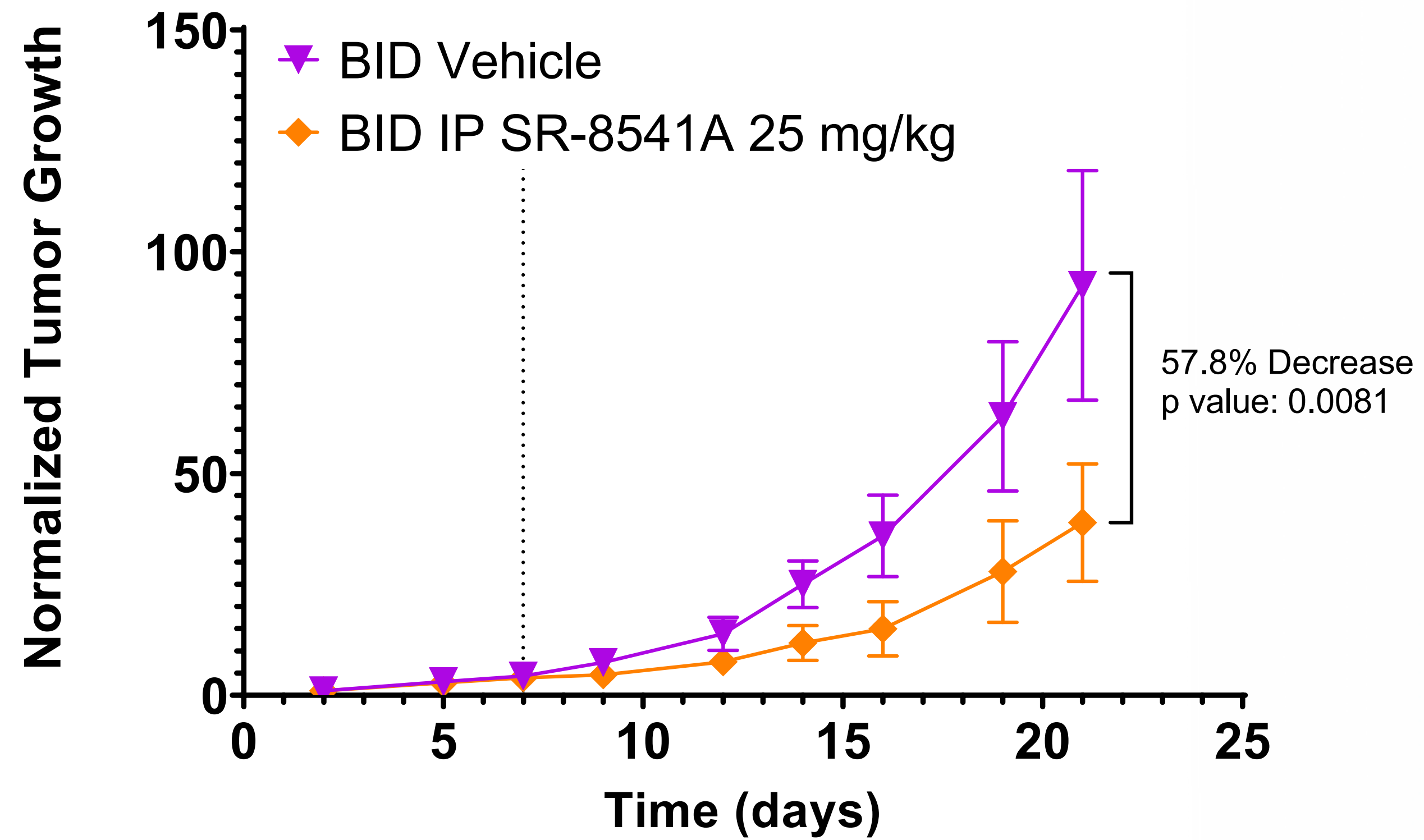


# LOSS OF HOST ENPP1 SLOWS TUMOR GROWTH AND PROLONGS SURVIVAL OF MICE

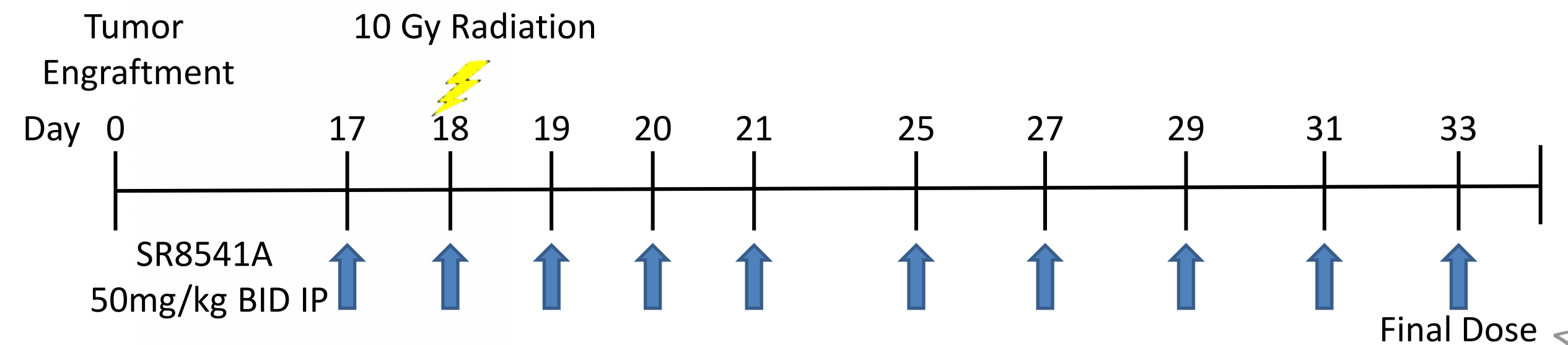
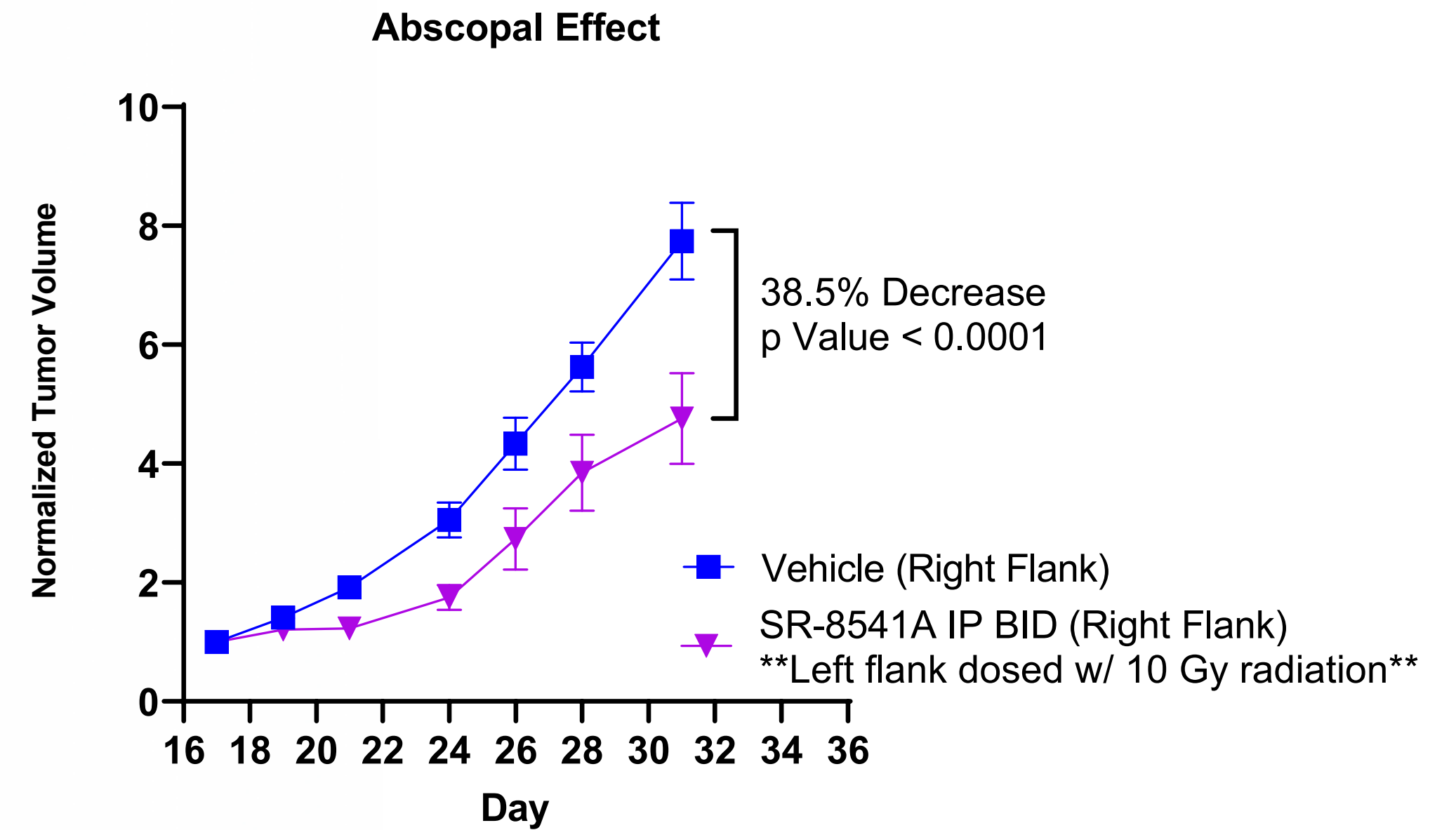
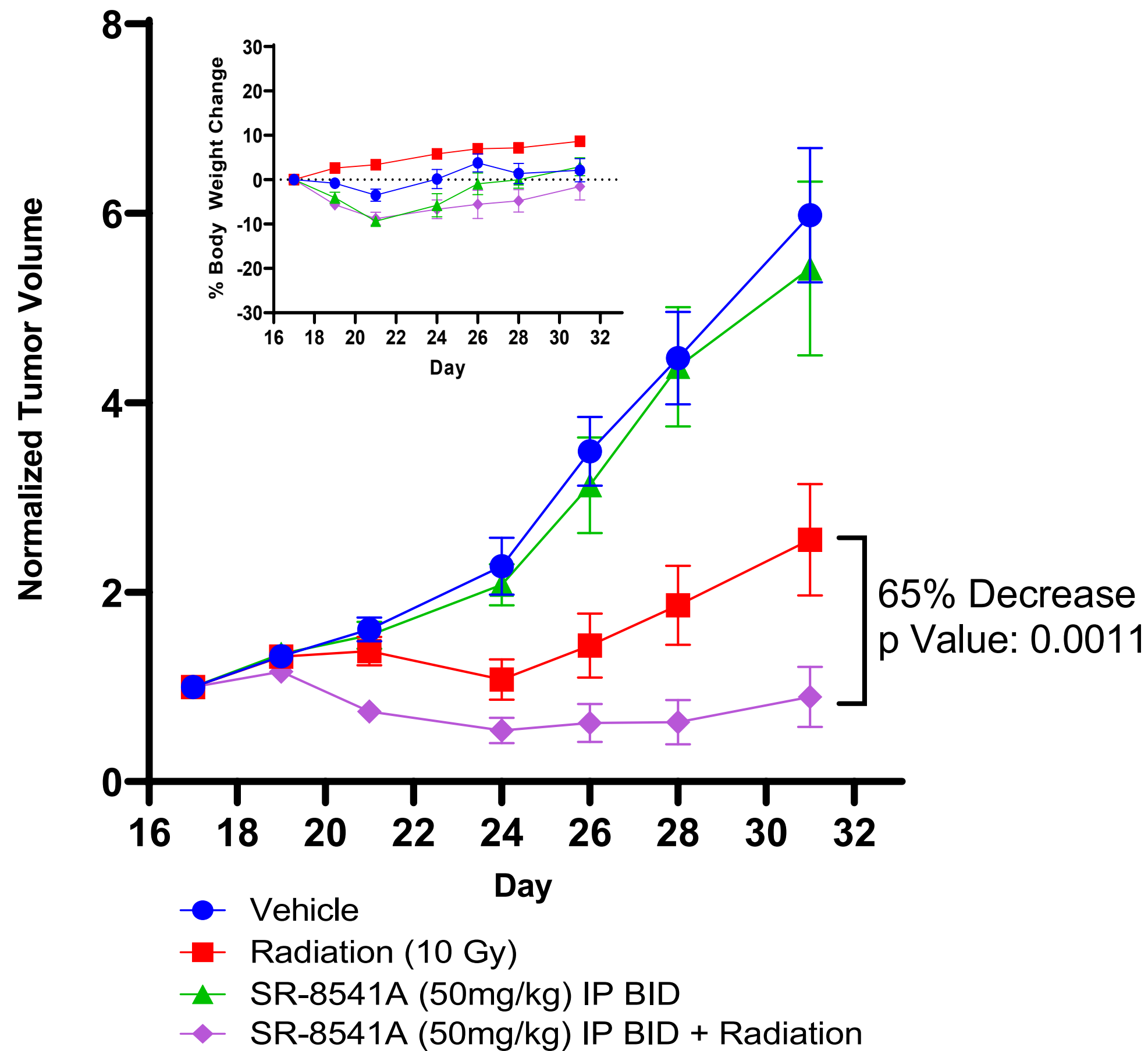


E0771 cells ( $5 \times 10^4$ ) were orthotopically injected into WT ( $n = 10$  mice) or *Enpp1*<sup>-/-</sup> ( $n = 6$  mice) C57BL/6J mice.

# SR-8541A: CT26 COLON CANCER MODEL



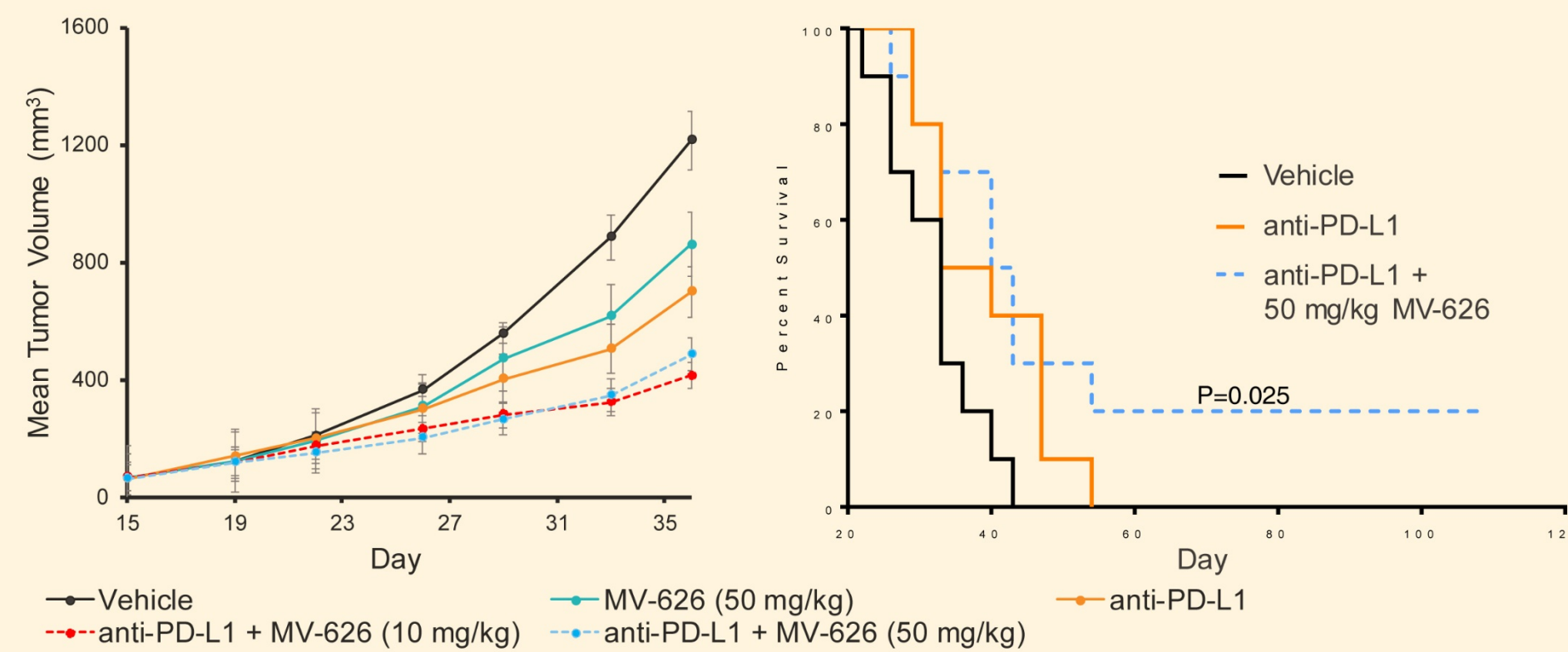
# SR-8541 TREATMENT AND RADIATION THERAPY DEMONSTRATE SYNERGY AND ABSCOPAL ANTI-TUMOR RESPONSE IN A MC38 MODEL





# ENPP1 INHIBITORS DEMONSTRATE SYNERGY WITH PD-L1

## MV-626 Shows Monotherapy Activity and Enhances anti-PD-L1 Efficacy in MC38 Tumor Model



- MAVU-626 was dosed at 50 mg/kg PO QD on days 15 -36; data presented as mean +/- SEM
- Anti-PD-L1 mAb (10 mg/kg) was dosed twice weekly x 6 doses beginning on day 14
- Only anti-PD-L1 + 50 mg/kg MAVU-626 group had survival with  $p < 0.05$  vs vehicle (Wilcoxon; no animals were censored)

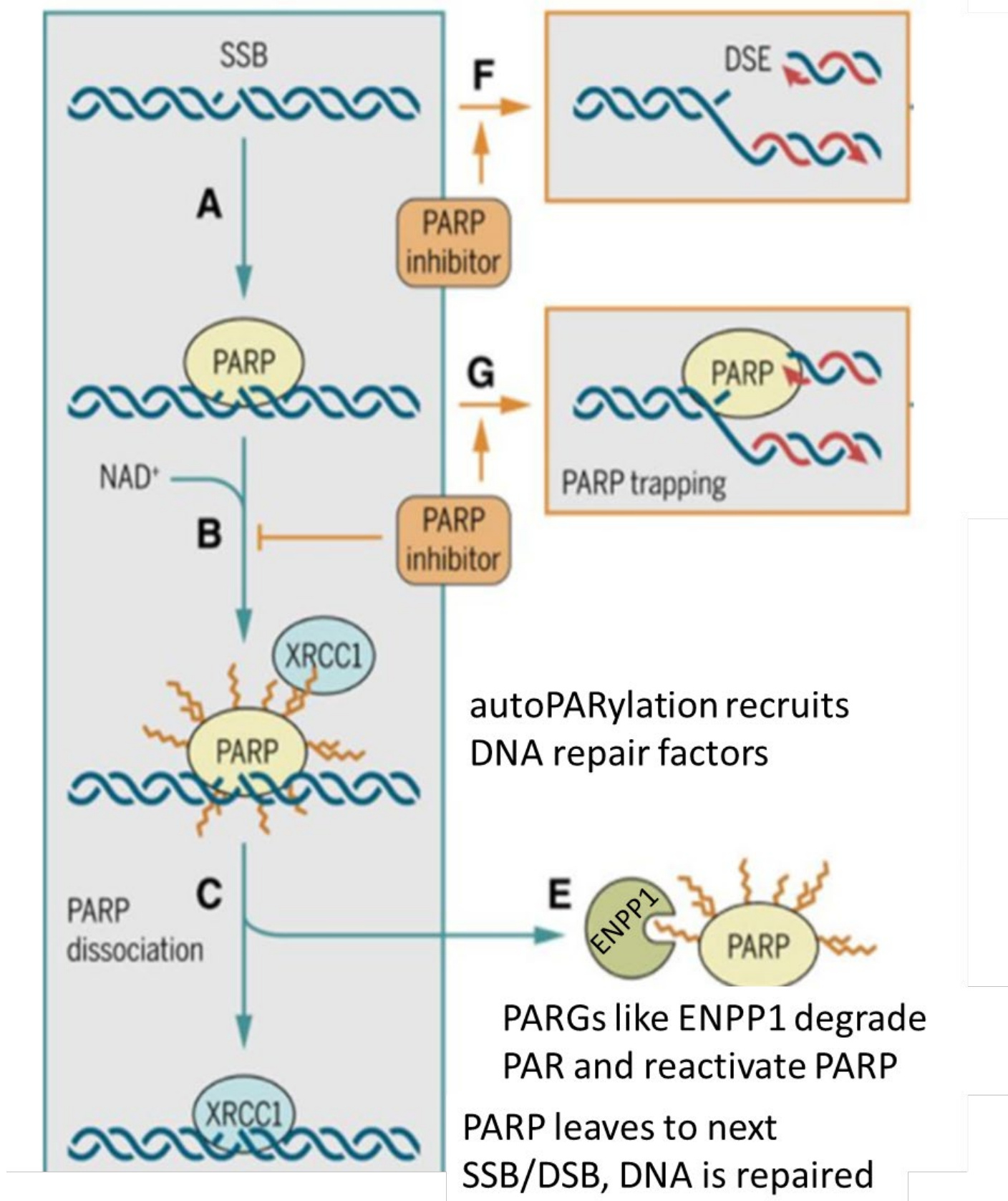
- Data from Mavupharma poster at SITC

- Our Advantages:

- More potent and specific compounds from IP analysis
- Several scaffolds each with single digit nanomolar compounds
- DMPK characteristics

*Stingray is doing checkpoint combination studies now*

# SYNERGY WITH PARP INHIBITION



	Drug treatment	CI Values		Chou-Talalay
			ED50	
MDA-MB-468 (BRCA1 wild type)	SR-8291:Olaparib	1:1	0.742	Slight Synergy
		10:1	0.847	Slight Synergy
		1:10	0.258	Synergy
	SR-8314:Olaparib	1:1	0.393	Synergy
		10:1	0.609	Slight Synergy
		1:10	0.475	Synergy
	SR-8343:Olaparib	1:1	0.328	Synergy
		10:1	0.322	Synergy
		1:10	0.375	Synergy
MDA-MB-436 (BRCA1 mutant)	SR-8291:Olaparib	1:1	1.119	No Synergy
		10:1	0.927	No Synergy
		1:10	0.977	No Synergy
	SR-8314:Olaparib	1:1	1.351	No Synergy
		10:1	1.222	No Synergy
		1:10	1.956	No Synergy
	SR-8343:Olaparib	1:1	1.001	No Synergy
		10:1	0.724	Slight Synergy
		1:10	0.375	Synergy

# ENPP1 INHIBITOR CLINICAL DEVELOPMENT PROGRAM

## **Single Agent:**

- Single agent activity in interferon responsive tumors
  - (CTCL, Myelofibrosis etc.)
- Single agent activity in immune responsive tumors
  - MSI high cancers

## **Combinations:**

- Checkpoint inhibitors
- Anti-CD38 antibody in Multiple Myeloma
- PRRT
- PARP inhibitors
- Chemotherapy
- CAR-T and CAR-NK cells



# Business Aspects



**STINGRAY**  
**THERAPEUTICS**

# RECENT INNATE MODULATOR ONCOLOGY EXITS

## Sellers:



## Buyers:



## Technology:

**Innate Immunity Modulators  
Oncolytic Viruses**

Average Upfront:  
**\$230 MM**

Average Milestones:  
**\$950 MM**

# ONE DIRECT COMPETITOR BOUGHT JULY 2019!

**FRAZIER** HEALTHCARE  
PARTNERS

**\$20M Investment**

– ownership 67.8%–

**Mavu**  
PHARMA

**ENPP1 inhibitor**

– in preclinical development –  
(Slightly ahead of Stingray)

**abbvie**

July 2019:

**\$300M+**

(Estimated / Price  
undisclosed)

**We should be next!**












- **Stingray now the Next ENPP1 program available in development.**
- **Pharma often buys the top 3 or 4 in a category.**
- **Example: Glaxo purchase of Tesaro PARP inhibitor (#4) for \$5.1B in Dec. 2018.**

# FULL COMPETITIVE LANDSCAPE







## Intra-Tumoral

 BMS-986301 (IFM Uno), IT & IM Phase 1	 Reverse merged into Chinook, ADU-S100 de-resourced, rtnd by Novartis Ph 2	 MK-1454, MK-2118 De-resourced after Phase 1-2	 JNJ-67544412 Preclinical	 BI-STING Preclinical	~30 other intra-tumoral direct STING agonism programs
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## Systemic

 - Phase 1 IV – Reverse merger into F-Star for \$30M cash, \$20M contingent rights on SB11285	 Claim IV/SubQ STING agonism. IMSA101 - Phase 1 as IT -	 Small molecule STING agonism program. - Preclinical -	 Small molecule STING agonism program. - Preclinical -	 STING agonist Antibody Drug Conjugates program. - Preclinical -	 ExoSTING Exosome STING agonist program. - Preclinical -
 IV GSK3745417 Phase 1	 JNJ-6196 IV STING agonist	 Oral MSA-2, De-resourced after Preclinical	 Small molecule direct STING agonism. TTI-10001, Preclinical – divesting	 Program in direct STING agonism. - On hold -	

## ENPP1 Inhibitor

  MV-626 Oral - Still Preclinical -	 SR-8541a Oral - Preclinical -	 (Stanford) ANG-1623 IV/SubQ No oral prodrug - Preclinical -	 Early preclinical	 Early preclinical
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# INTELLECTUAL PROPERTY

1

## **First Patent covers 8200 compounds - Pending**

- Provisional filed July 27, 2017 and perfected July 2018
- 0.25% royalty to Huntsman Cancer Institute

2

## **Second Patent covers 8300-8330 compounds - Pending**

- Provisional filed August 1, 2018 and perfected August 1, 2019
- Fully owned by Stingray; no economic obligations

3

## **Third Patent covers 8340-8550 compounds - Provisional**

- Provisional filed March 20, 2019
- Fully owned by Stingray; no economic obligations

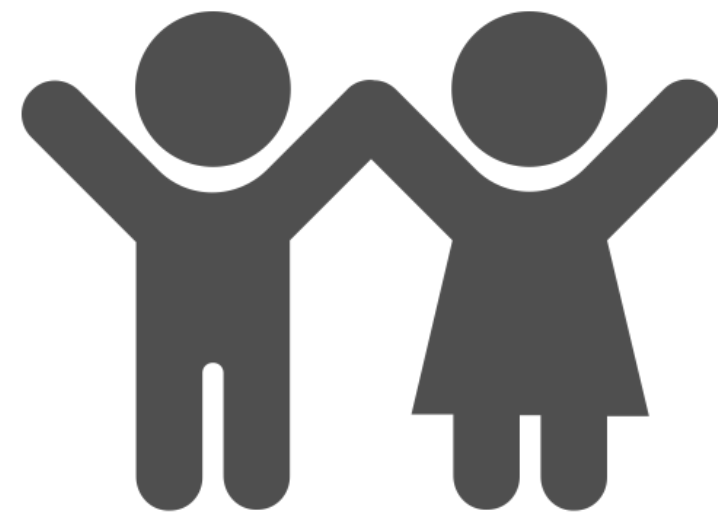
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## **Fourth Patent covers 8500-8600 compounds - Provisional**

- Provisional filed February 5, 2020
- Fully owned by Stingray; no economic obligations



# AS AN INVESTOR, CONSIDER THE BENEFITS:



Invest in a major impact drug that may change lives.



Join a proven team that's repeating their model.

**10-35x**

Biotech is lucrative when it returns.

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**+1 317.517.9500**