Targeting Innate Immunity

ENPP1 inhibition

Having both arms of the immune system in the fight against cancer

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 tolerability and toxicology is safe (rat and dog)

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“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
  - Many life-threatening cases also have auto-antibodies to interferon

Auto-antibody Diseases

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

STINGRAY THERAPEUTICS

OUTSTANDING BIOTECH SPECIALISTS, FROM DISCOVERY THROUGH PHASE 2

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

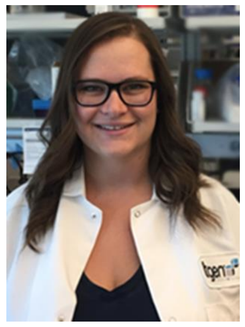
Jon Northrup
CEO & Co-Founder

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

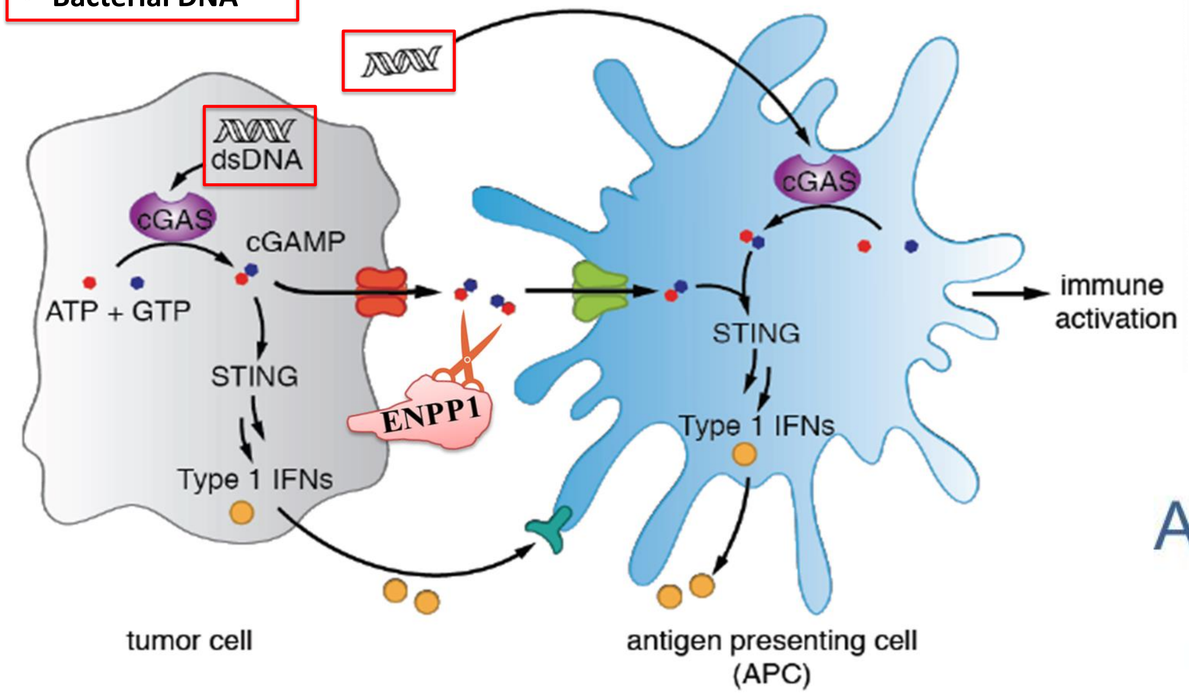
SCIENCE AND DEVELOPMENT

STINGRAY THERAPEUTICS

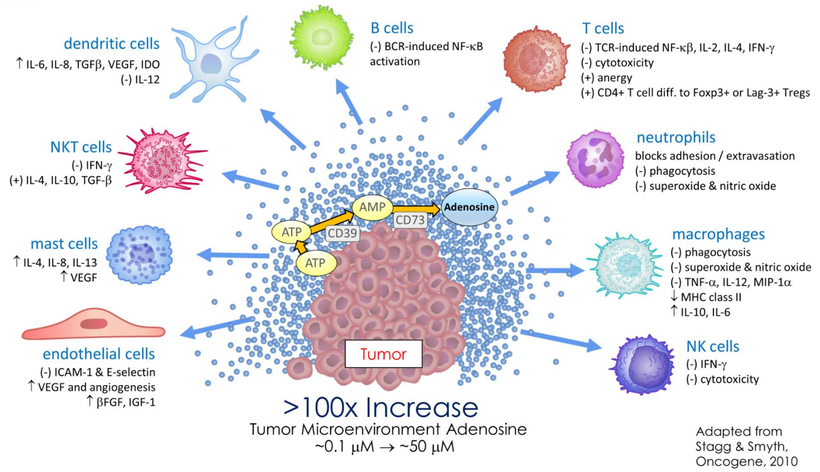
ENPP1 INHIBITION: IMPORTANT IN INNATE AND ADAPTIVE IMMUNITY

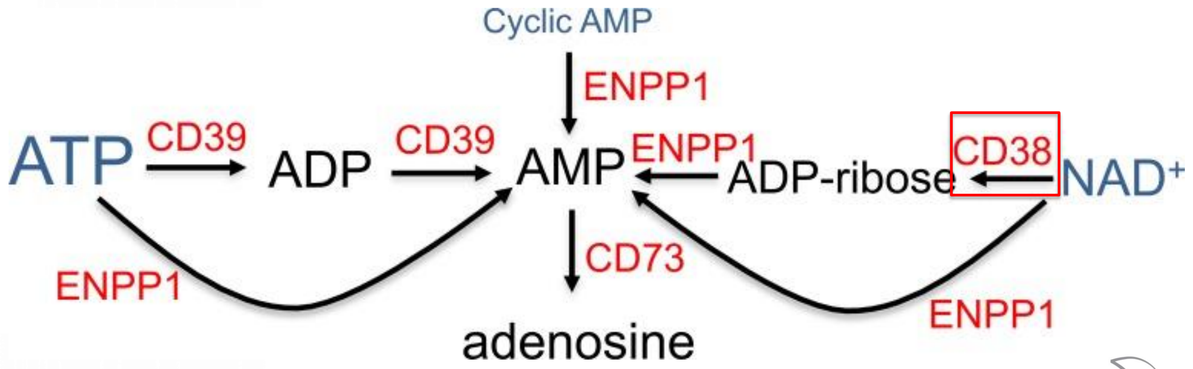
Regulates STING-dependent innate immune response

- **Tumor DNA**
- **Viral DNA**
- **Bacterial DNA**



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





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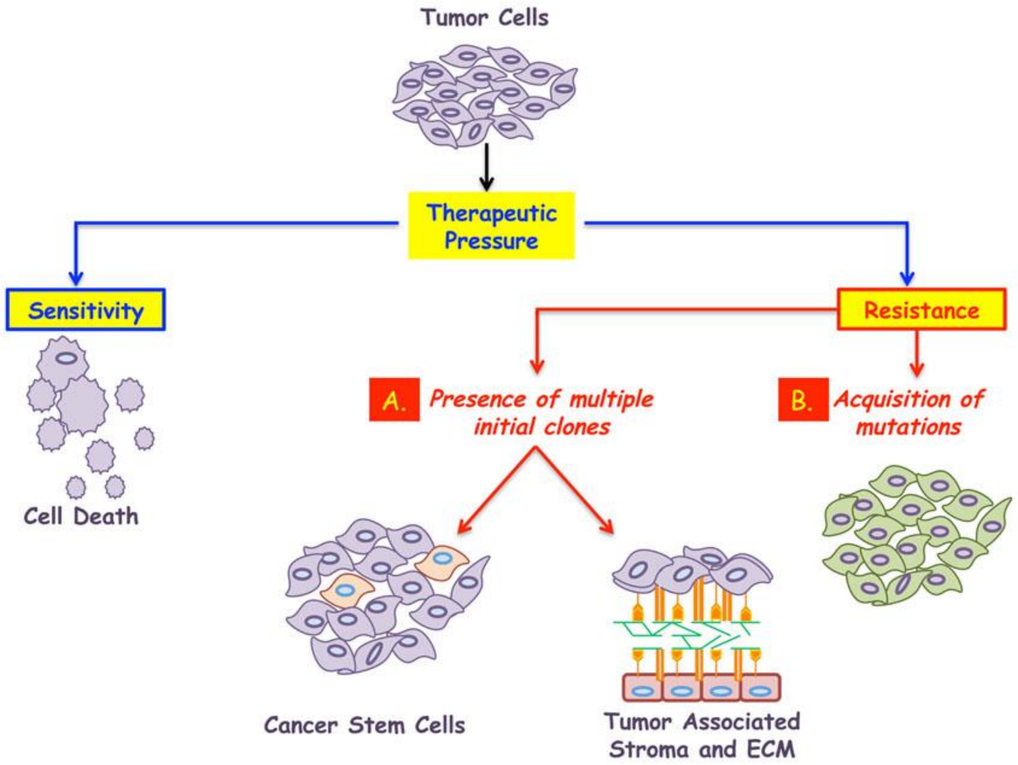
INNATE IMMUNE RESPONSE IS TIED TO CHEMO RESISTANCE



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.

Stem cell characteristics in glioblastoma are maintained by the ENPP1
(Cell Death Differ. 2014 Jun;21(6):929-40)

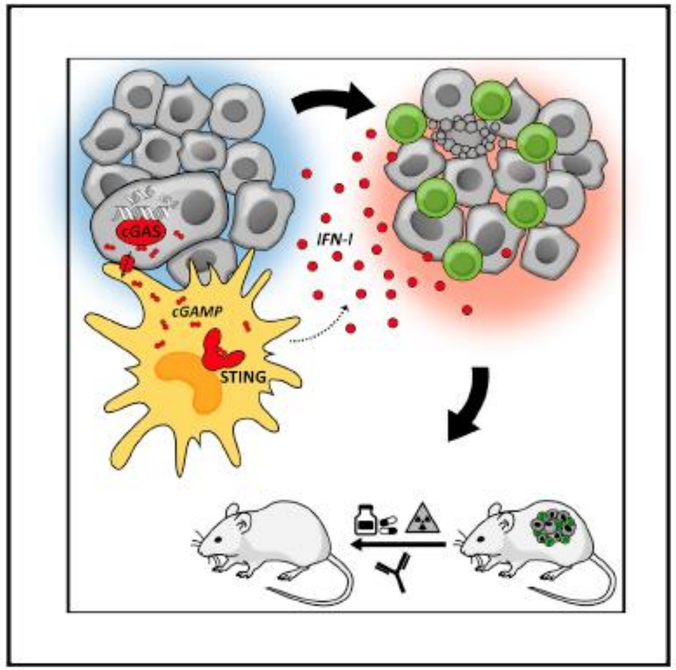
Loss of microRNA-27b contributes to breast cancer stem cell generation by activating ENPP1
(Nat Commun. 2015 Jun 12;6:7318)

ENPP1 interacts with ABCG2 and promotes it's surface localization

ENPP1 knockdown increases chemosensitivity

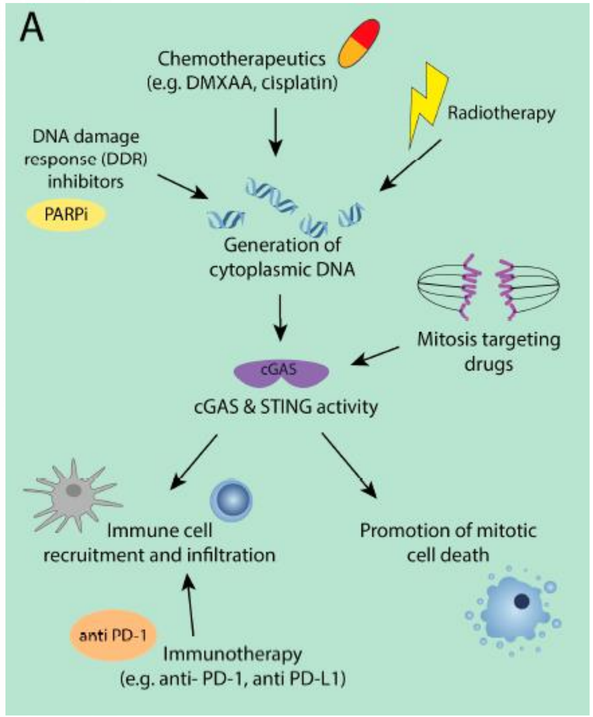
ENPP1 processes protein ADP-ribosylation in vitro
(FEBS J. 2016 Sep;283(18):3371-88)

Cancer Cell Intrinsic cGAS Expression Mediates Tumor Immunogenicity



Highlights

- cGAS in cancer and STING in host cells are minimal requirements to activate CD8$^+$ 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

cGAS/STING/Interferon activate T cells and improve Immunogenicity of the tumor

STINGRAY THERAPEUTICS

CLINICAL CANDIDATE SCAFFOLDS

Scaffold 1 – ENPP1 inhibitors
- Lead candidate: SR-8541A (5 nM)
- Selective
- Provisional filed Feb 5, 2020

Scaffold 2 – ENPP1 inhibitors
- SR-8542-3 (6 nM)
- Selective
- Provisional filed Dec 2, 2020

Scaffold 3 – ENPP1/CdnP dual inhibitors
- SR-8727 (9 nM / 14 nM)
- Selective
- Provisional filed Dec 9, 2020

Latest Patents

- Fully owned by Stingray; no economic obligations

- Chemically distinct, independent scaffolds each with clinical candidates

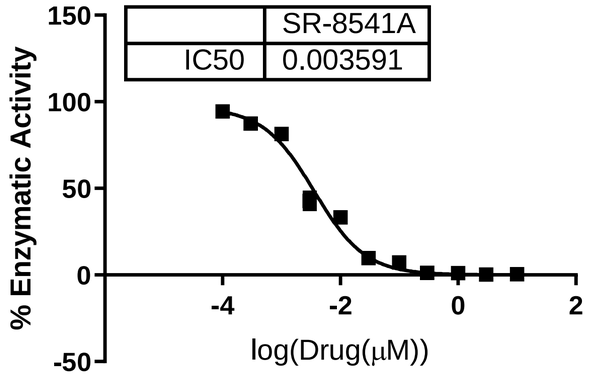
Fresh IP, Deep Chemistry, No siphoning of economics to a third party

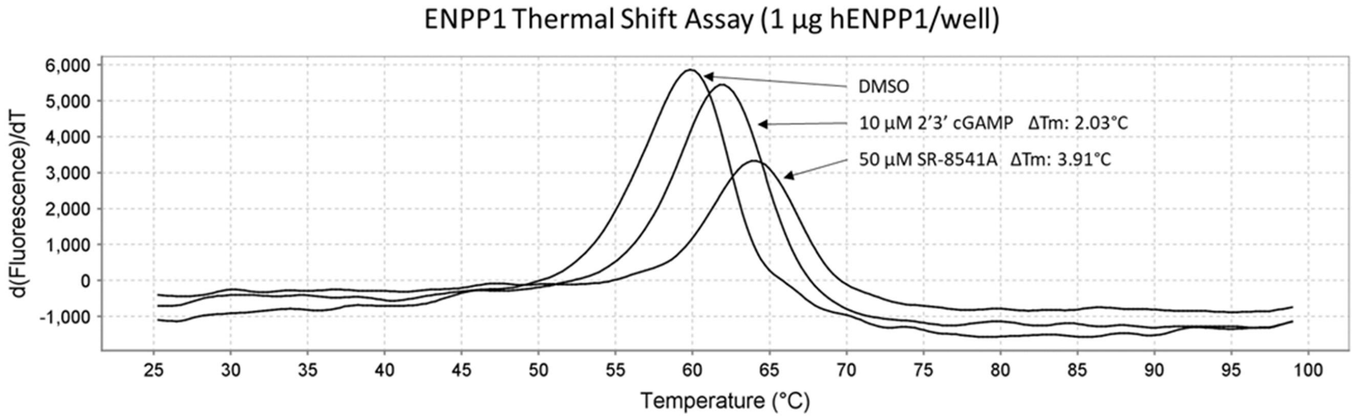
STINGRAY THERAPEUTICS

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

ENPP1 enzymatic assay

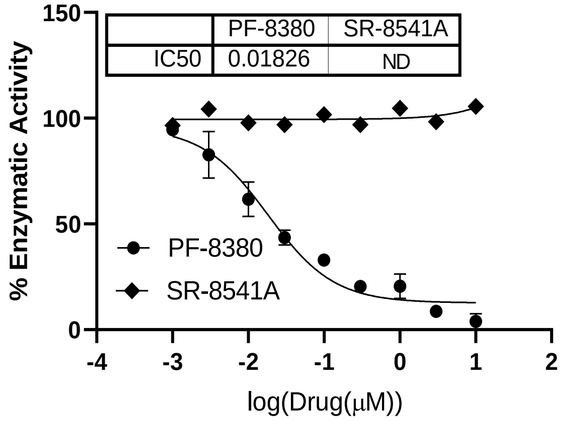
	SR-8541A
IC50	0.003591



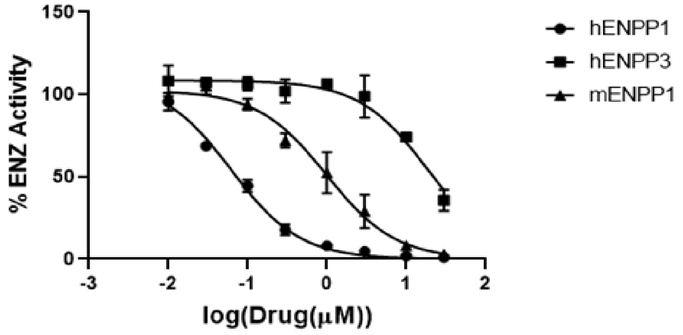


ENPP2 enzymatic assay

	PF-8380	SR-8541A
IC50	0.01826	ND



Cell-based ENPP enzymatic assay



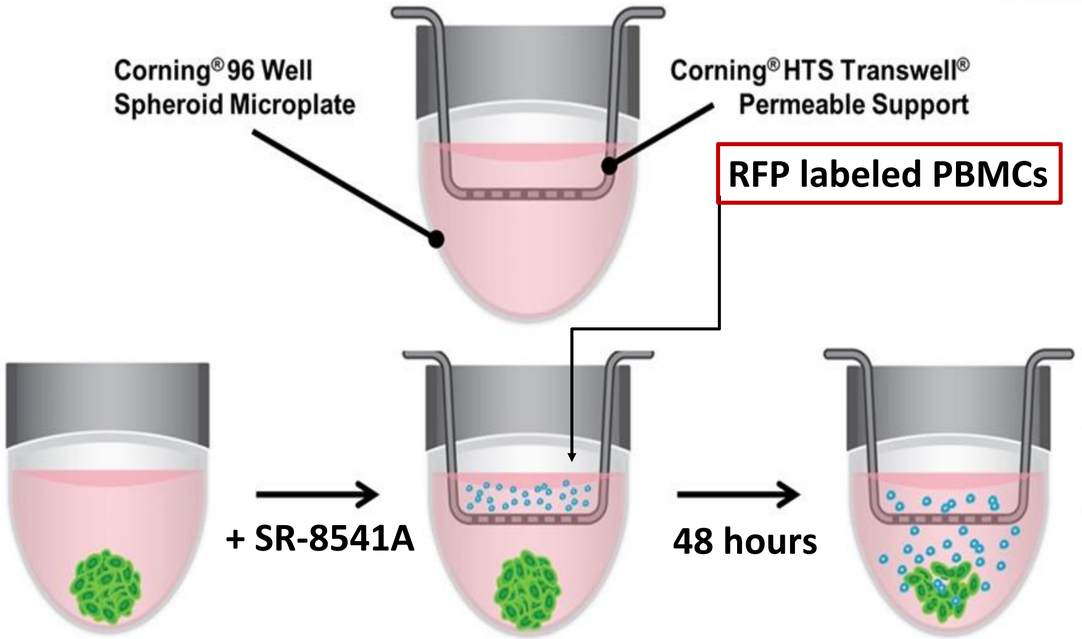
	hENPP1	hENPP3	mENPP1
IC50	0.06217	18.80	0.9865

- 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

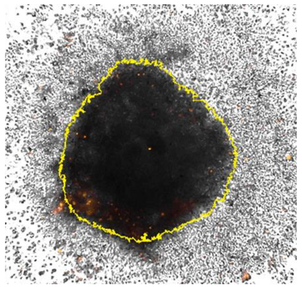
4 nanomolar potent, tightly bound to target, no known interactions with off targets

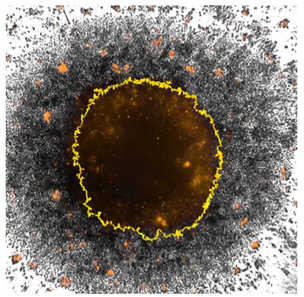
STINGRAY THERAPEUTICS

IMMUNE INFILTRATION ASSAY

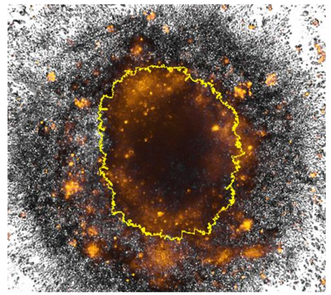


DMSO





Drug (X µM)



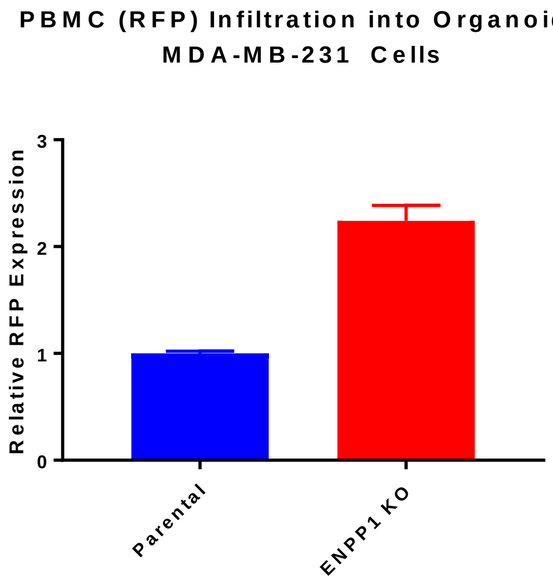
Drug (2X µM)

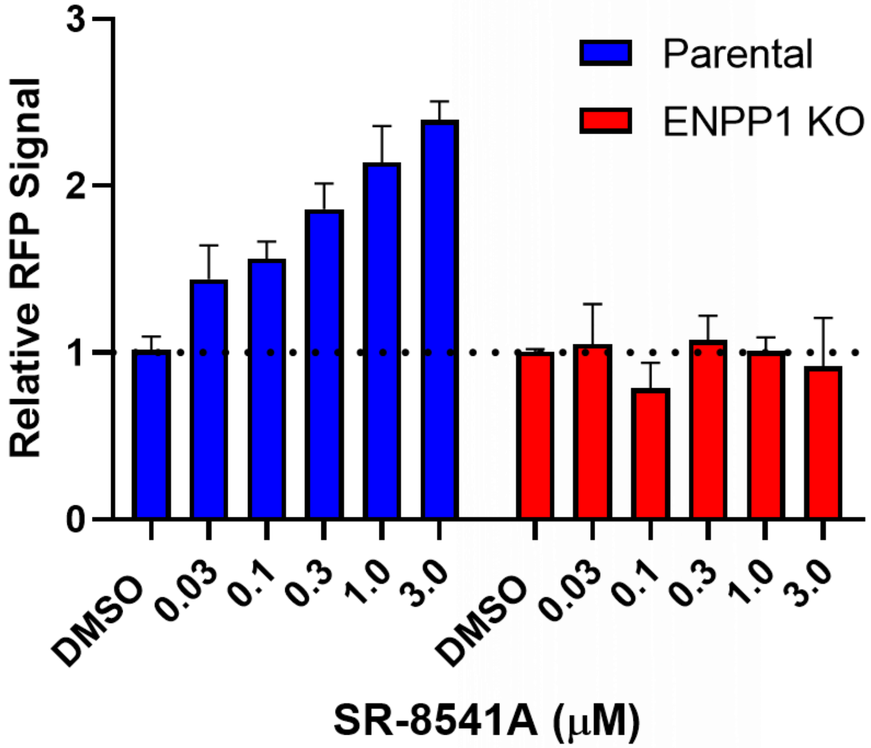
Cytokines secreted in medium
Gene expression changes in spheroid
immune cell infiltration and tumor death

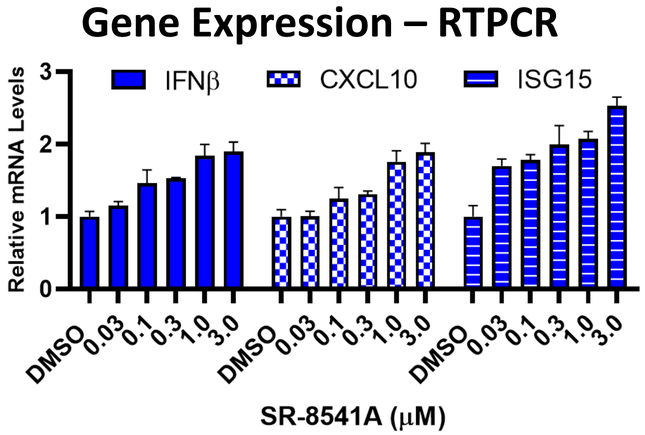
We turn "cold" tumors "hot", immune cells infiltrate and kill

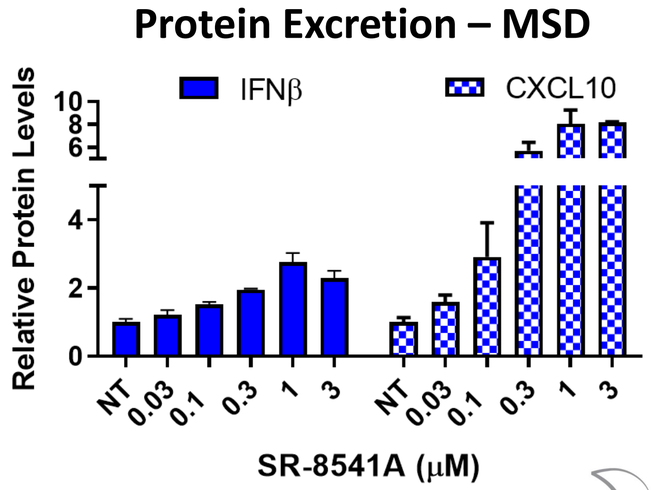
STINGRAY THERAPEUTICS

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







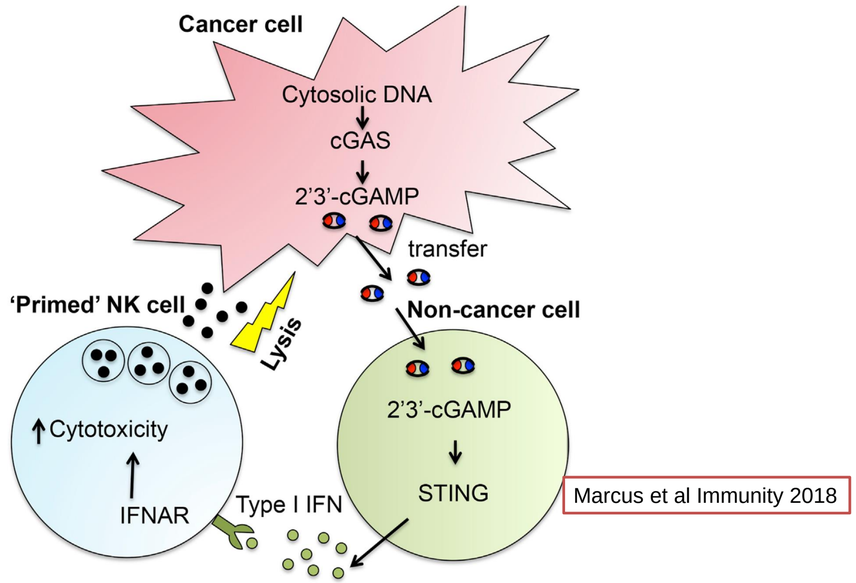


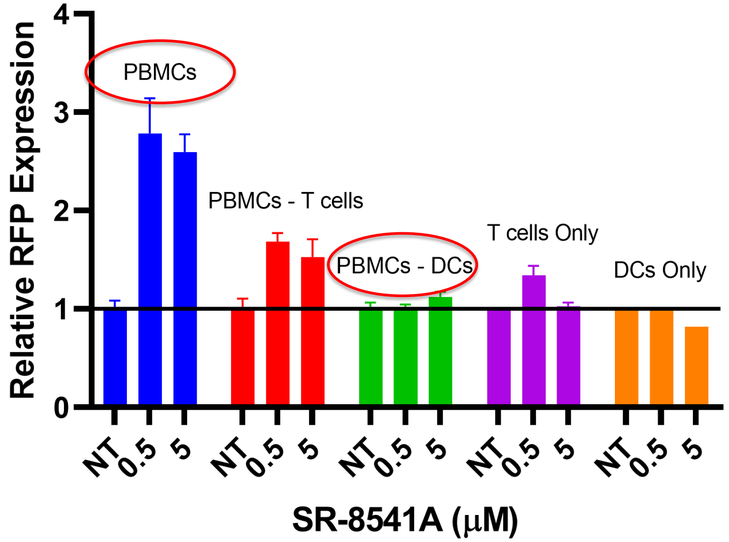
Dose dependent response and downstream activation of biomarkers

STINGRAY THERAPEUTICS

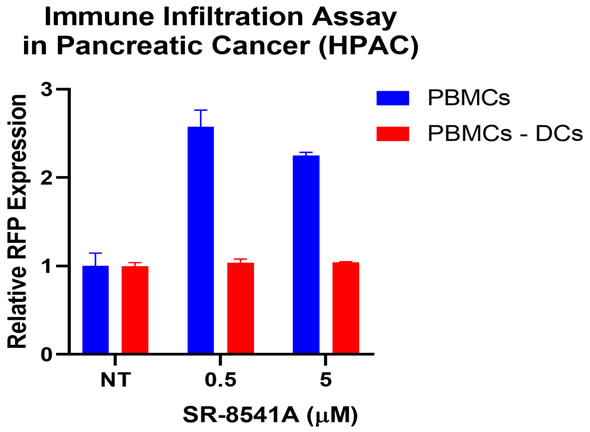
WHICH CELLS ARE REQUIRED FOR INFILTRATION?

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





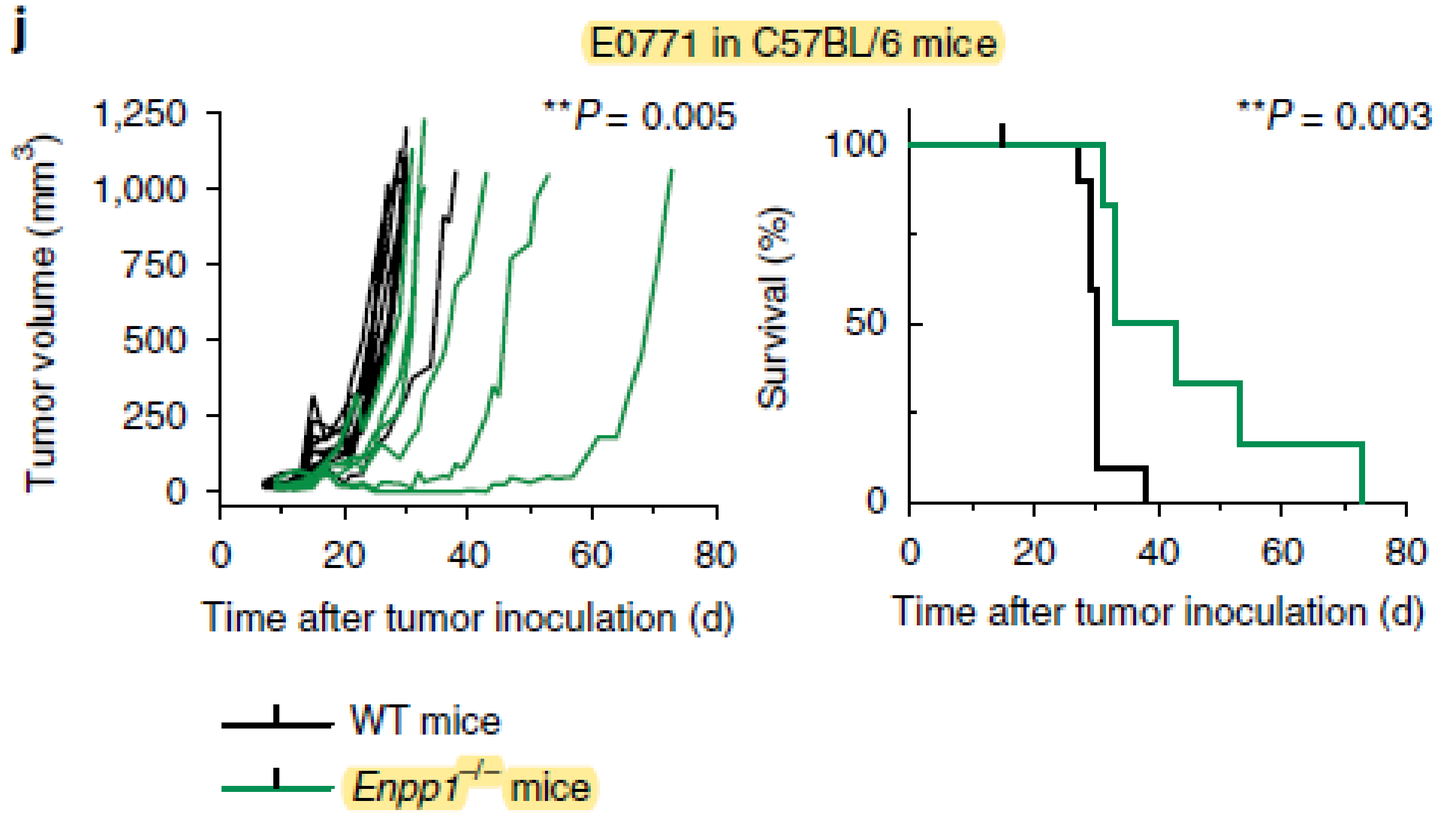
NK cells only stained



Natural Killer cells are strongly primed by SR-8541a activity

STINGRAY THERAPEUTICS

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

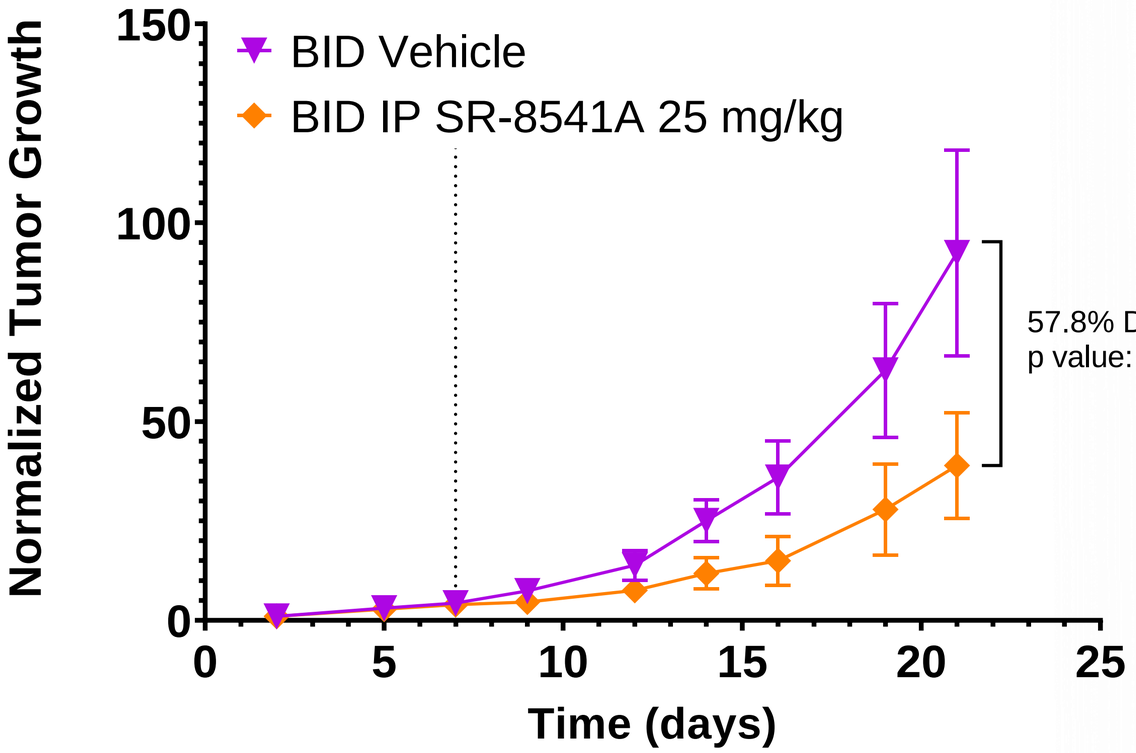


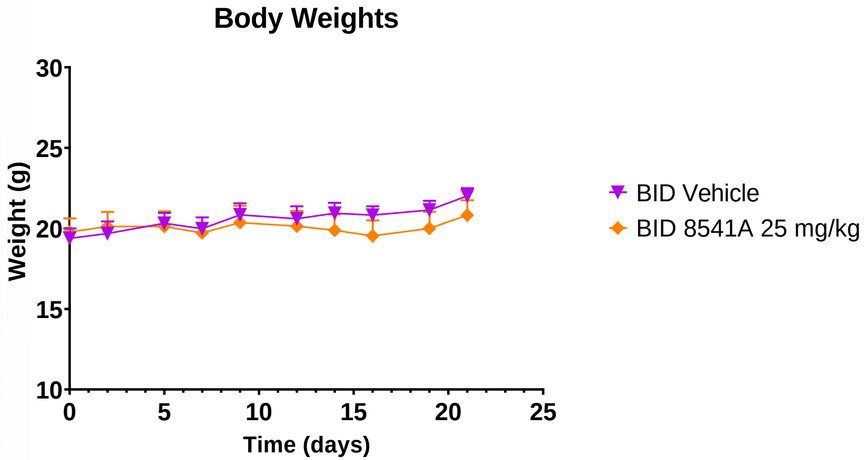
E0771 cells (5×10^4) were orthotopically injected into WT (n = 10 mice) or *Enpp1*−/− (n = 6 mice) C57BL/6J mice.

Knocking out ENPP1, like inhibiting it, prolongs survival and slows tumor growth

Nature Cancer | VOL 1 **184** | February 2020 | 184–196 |

SR-8541A: CT26 COLON CANCER MODEL

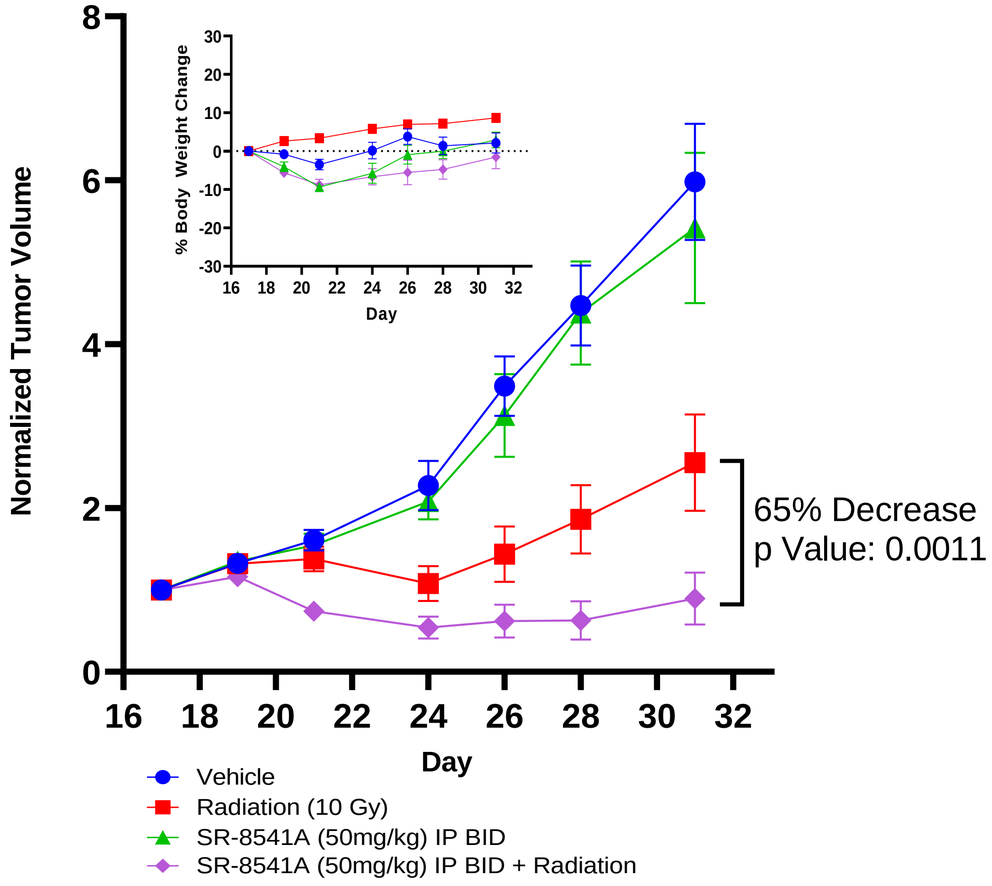


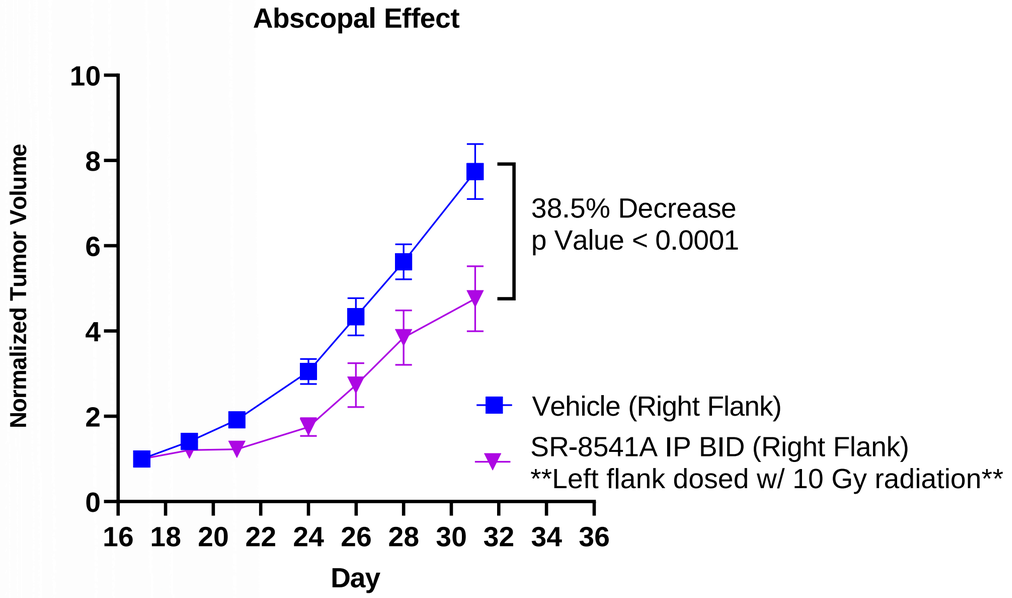


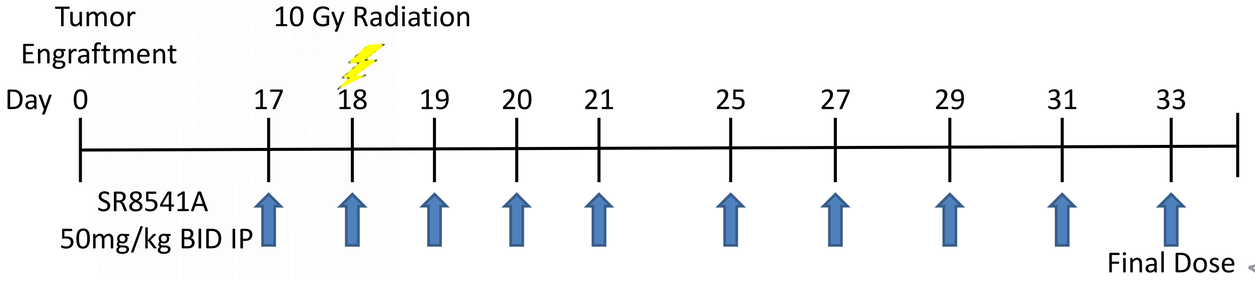
Our first single agent study <u>at low dose</u> shows almost 60% tumor growth suppression

STINGRAY THERAPEUTICS

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

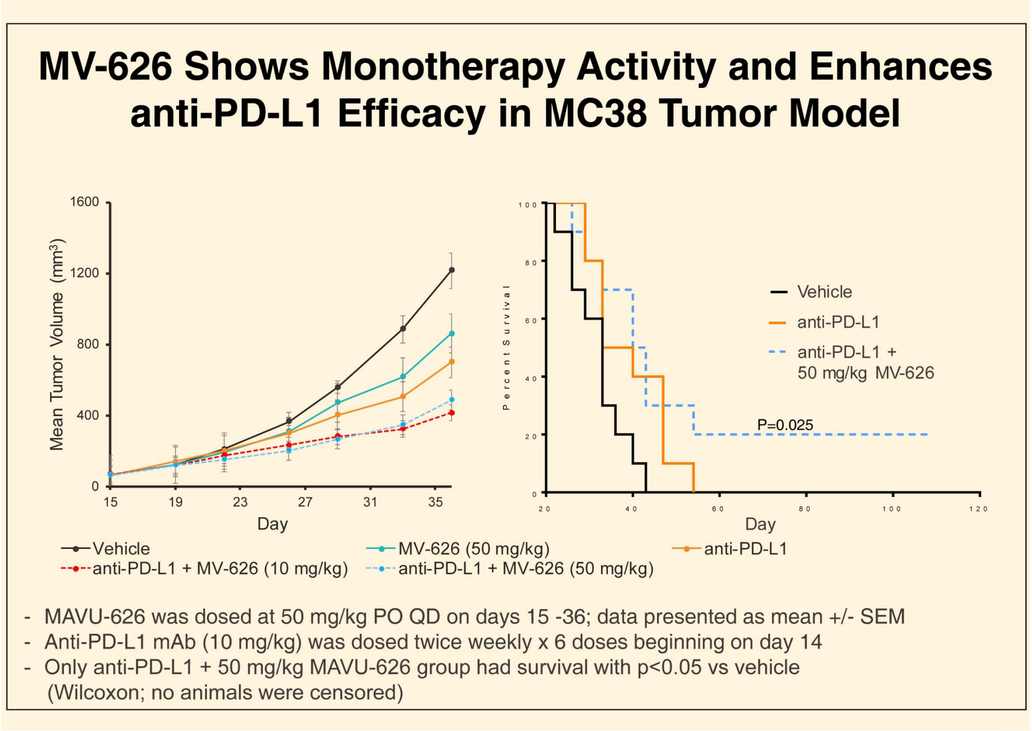






In combo, almost flat-lining the tumor and a strong single agent abscopal effect

ENPP1 INHIBITORS DEMONSTRATE SYNERGY WITH PD-L1



- Data from Mavupharma poster at SITC

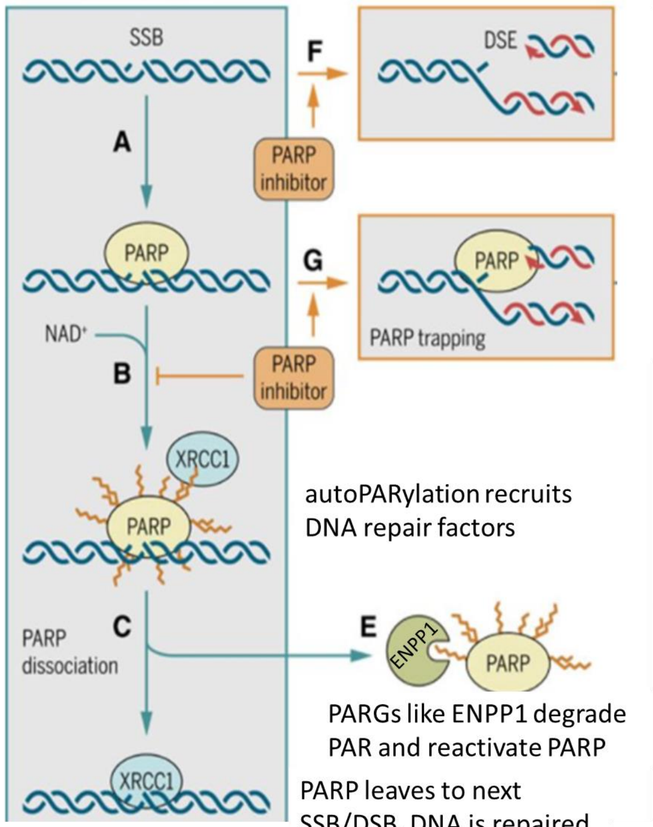
- *Our Advantages:*
- More potent and specific compounds from IP analysis
- Several scaffolds each with single digit nanomolar compounds
- DMPK characteristics

Stingray is doing checkpoint combination studies now

We expect strong efficacy with checkpoint inhibitors

STINGRAY THERAPEUTICS

SYNERGY WITH PARP INHIBITION



Palazzo et al 2016

	Drug treatment		CI Values ED50	Chou-Talalay
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

	Drug treatment		CI Values ED50	Chou-Talalay
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 inhibition should be synergistic with PARP inhibition

STINGRAY THERAPEUTICS

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 (microsatellite unstable) high cancers

Combinations:

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

We have single agent responsive tumors and a broad potential in combination

STINGRAY THERAPEUTICS

Business Aspects

STINGRAY THERAPEUTICS

RECENT INNATE MODULATOR ONCOLOGY EXITS

Sellers:

ViraTherapeutics

BeneVir

Viralytics
Developers of Oncolytic Immunotherapies

RIGONTEC

IFM THERAPEUTICS

ADURO BIOTECH

MaVu PHARMA

Buyers:

Boehringer Ingelheim

Johnson & Johnson

MERCK

NOVARTIS

abbvie

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.**

STING COMPETITIVE LANDSCAPE - SUMMARY

- **Intra-tumoral STING agonist programs have virtually ALL failed**
  - Lack of abscopal effect makes them clinically unacceptable
  - Would have to inject every tumor

- **Systemic STING agonist programs are failing due to toxicity**
  - Mersana reports preclinical toxicity with GSK systemic diABZi IV STING agonist
  - Merck publishes all chemistry and biology on their systemic oral STING agonist
  - J&J stops their systemic IV STING agonist
  - Springbank forced into reverse merger with F Star, unable to finance their program

- **ENPP1 programs are moving forward – no failures**
  - Abbvie/Mavupharma and Stingray tied for first to clinic
  - All other programs without oral clinical candidates
  - Volestra (Lou Cantley lab/ Weill Cornell Medicine) rumored to have ENPP1 inhibitor program
  - Raphael Capital starting ENPP1 inhibitor company

- **Other programs with a twist**
  - Mersana ADC-STING Agonist may be sufficiently targeted to avoid toxicity
    - ADC targets not revealed
  - Codiak Exosome encapsulated STING agonist

STING COMPETITIVE LANDSCAPE

STINGRAY THERAPEUTICS

Intra-Tumoral

- Bristol-Myers Squibb: BMS-986301 (IFM Uno), IT & IM, Phase 1
- ADURO BIOTECH: Reverse merged into Chinook, ADU-S100 de-resourced, rtnd by Novartis Ph 2
- MERCK: MK-1454, MK-2118 De-resourced after Phase 1-2
- Janssen: JNJ-67544412 Preclinical
- Boehringer Ingelheim: BI-STING Preclinical
- ~30 other intra-tumoral direct STING agonism programs

Systemic

- spring bank pharmaceuticals: - Phase 1 IV – Reverse merger into F-Star for $30M cash, $20M contingent rights on SB11285
- ImmuneSensor THERAPEUTICS: Claim IV/SubQ STING agonism. IMSA101 - Phase 1 as IT -
- Cancer Therapeutics CRC: Small molecule STING agonism program. - Preclinical -
- SILICON Therapeutics: Small molecule STING agonism program. - Preclinical -
- Mersana THERAPEUTICS: STING agonist Antibody Drug Conjugates program. - Preclinical -
- CODIAK: ExoSTING Exosome STING agonist program. - Preclinical -
- gsk GlaxoSmithKline: IV GSK3745417 Phase 1
- gsk GlaxoSmithKline: IV GSK diABZi Phase 1
- Janssen: JNJ-6196 IV STING agonist
- MERCK: Oral MSA-2, De-resourced after Preclinical
- TRILLIUM THERAPEUTICS INC.: Small molecule direct STING agonism. TTI-10001, Preclinical – divesting
- NIMBUS THERAPEUTICS: Program in direct STING agonism. - On hold -

ENPP1 Inhibitor

- abbvie / Mavu PHARMA: MV-626 Oral - Still Preclinical -
- STINGRAY THERAPEUTICS: SR-8541a Oral - Preclinical -
- Angarus THERAPEUTICS INC.: (Stanford) ANG-1623 IV/SubQ - Preclinical -
- Avammune THERAPEUTICS: Early preclinical
- Cancer Therapeutics CRC: Early preclinical
- volastra: Targeting chromosol instability Early preclinical

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 - Pending

- Provisional filed March 20, 2019 and perfected March 17, 2020
- Fully owned by Stingray; no economic obligations

4

Fourth Patent covers SR-8541a compounds - Provisional

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

5

Fifth Patent covers SR-8542-3 compounds - Provisional

- Provisional filed December 2, 2020
- Fully owned by Stingray; no economic obligations

6

Sixth Patent covers SR-8727 compounds - Provisional

- Provisional filed December 9, 2020
- Fully owned by Stingray; no economic obligations

STINGRAY THERAPEUTICS

BRIDGE CONVERTIBLE NOTE OPEN NOW

- Previous $2 M Seed Series raised
- **Targeting a $1.5 M Bridge Raise, $1/2 M received to date (open 3 months)**
- Terms
  - 5% interest rate
  - 20% discount into Series A
  - Capped at $16 M pre-money conversion
- To be used for (Oct.'20 – May '21)
  - In vivo tumor models – high dose, combinations
  - Complete IND enabling activities (IND scheduled for 4/21)
  - Fast start on first in man

STINGRAY THERAPEUTICS

AS AN INVESTOR, CONSIDER THE BENEFITS:

STINGRAY THERAPEUTICS

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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