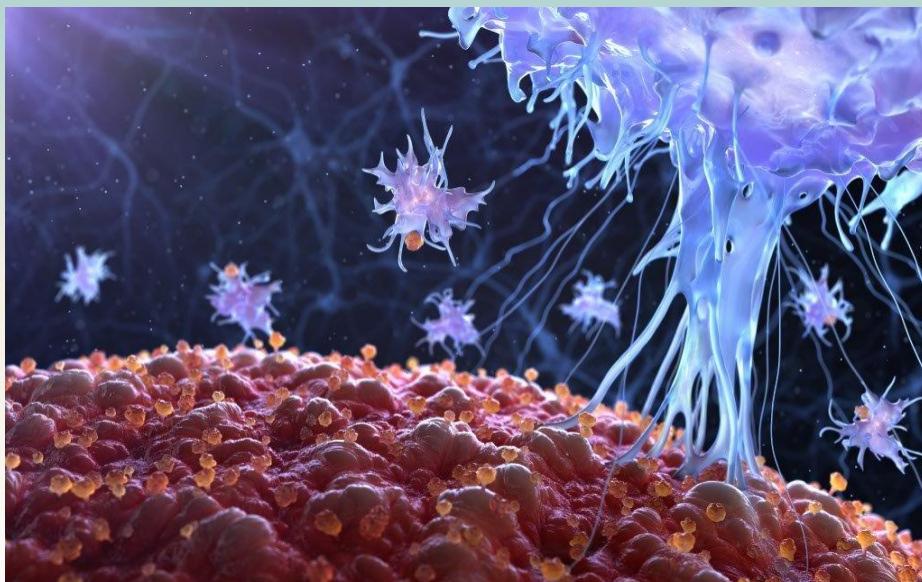


# Improving Lives of Patients with Cancer



*The Innova therapeutic platform consisting of various molecules targeting SFRP2 is being developed to treat various cancers and fibrosis. In addition, a diagnostic biomarker is being developed to assess SFRP2 levels in the blood for early cancer detection and monitoring for efficacy and recurrence.*

*“The cancer treatment platform, based on 30 years in the pharmaceutical industry where my primary focus was on development of cancer treatments, has the highest potential in my view to change the paradigm of treatment of patients with many types of solid and hematological cancers, resulting in long term survival. Given the extensive global patent protection through 2042 and beyond, the commercial value of this platform is high, both as monotherapy and in combination.”*

*Dr. Robert Ryan, CEO*

# Investment Highlights: IVT-8086 (lead mAb) - An Exciting Novel Anticancer Therapy

**Monoclonal Antibody (mAb)  
Platform Selectively Targeting  
Secreted Frizzled-Related Protein-2  
(SFRP2), Which is a Secreted  
Protein Overexpressed in Various  
Cancers**

**Highly Experienced  
Management/Development Team  
with a Successful Track Record**

**Defined Regulatory Development  
Pathway and Robust IP Portfolio**

Lead humanized mAb selected, IVT-8086, has been shown to antagonize SFRP2 by selectively blocking the non-canonical Wnt/Ca<sup>2+</sup> pathway which significantly reduces tumor growth across multiple cancers

**Multi-faceted mechanism with DIRECT inhibition of Secreted Frizzled Related Protein 2 (SFRP2) in cancer:**

- Reduced tumor growth (primary and metastatic disease), including increased apoptosis of tumor cells
- Reduced angiogenesis, tumor cell migration and metastasis
- Rescues T Cell dysfunction including T Cell exhaustion, impacting expression of PD-1 and CD-38
- **Reduction in SFRP2 levels that are overexpressed in cancer**
- Impacts tumor associated macrophages (TAMs) by shifting balance to increase M1 “attack” TAMs and IFN- $\gamma$

- First biotech management team to obtain “Breakthrough Therapy” designation from the FDA for their therapeutic product
- **Same management team from previous company, Scioderm.**
  - 4<sup>th</sup> largest venture capital (VC)- backed exit in biotech/pharmaceutical space - \$22M total spend with exit deal totaling appr \$957M within 2.5 years of company initiation
- Selected as one of the “Fierce Top 15” by FierceBiotech, considered as one of the most promising emerging companies in the biotech industry

- Progress development of IVT-8086 into Phase 1 clinical trial in patients with advanced cancer to establish safety, tolerability and optimal treatment dose as a monotherapy and in combination
- Investigate IVT-8086 as targeted monotherapy treatment and in combination with anti-PD1 checkpoint inhibitors for cancers with high unmet need (sarcomas (including osteosarcoma (OS), pancreatic, multiple myeloma, and breast cancer including triple negative breast cancer)).
- **Osteosarcoma is a rare disease which was granted both orphan designation and rare pediatric disease designation from the FDA**
  - **Fast regulatory approval timeline, including opportunity to obtain a Rare Pediatric Disease priority review voucher (value range \$150-300M)**
- **Robust global patent portfolio, including composition of matter patents, active through 2042 and beyond**

# Innova Therapeutics is Led by an Experienced Senior Management Team with Extensive Global Development Experience...



**Robert Ryan, PhD**  
Chief Executive Officer

Founder & CEO of Innova Therapeutics and Former Co-Founder and CEO of Scioderm. Former Managing Director of Celtic Pharma and Celtic Therapeutics



**Ronald V. Nardi, Ph.D.**  
EVP Development

35+ years experience in drug discovery/development and regulatory affairs, Operational and management R&D experience in large pharma organizations and small/medium sized companies including start-up/biotechnology firms



**Nancy Klauber-DeMore, MD**  
Chief Scientific Officer

Professor of Surgery, Co-Leader Hollings Cancer Center Developmental Therapeutics Program Medical University of South Carolina (MUSC), and Program Director of the MD/PhD Program at MUSC. BMW Endowed Chair in Cancer Research, MUSC, Fellow, Judah Folkman Lab



**Michael Zimmer, MBA**  
Chief Financial Officer

Highly experienced executive brings 30 years of experience as a business leader in various roles including Finance, Accounting, Operations, Supply Chain, Business and Employee Development



**Willistine Lenon**  
EVP Clinical Operations

Highly experienced Clinical Operations Executive with 29+ years in the field of clinical research, including senior roles at major CRO and pharmaceutical companies

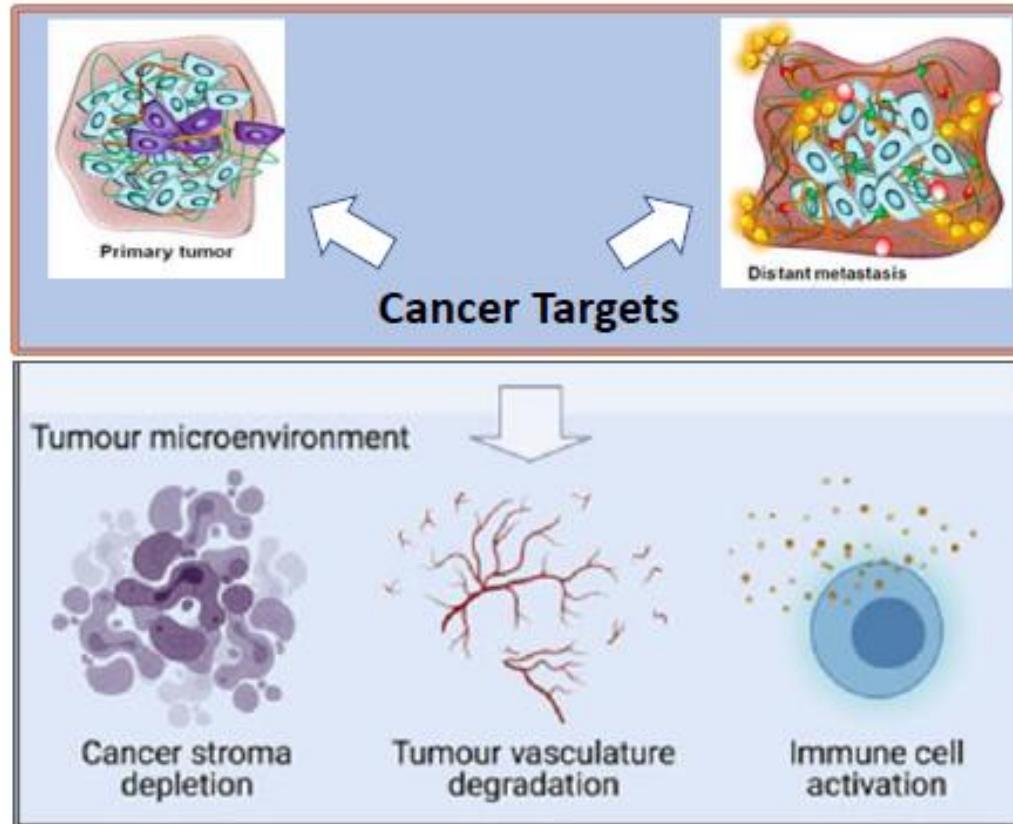


**Lisa Zimmerman**  
EVP of Regulatory Affairs, Compliance, and Quality  
Ms. Zimmerman is an accomplished drug developer with over 35+ years of industry experience. Lisa is an accomplished professional with a proven track record of success in Clinical Operations, Regulatory Affairs, Quality Assurance, and Regulatory Compliance.



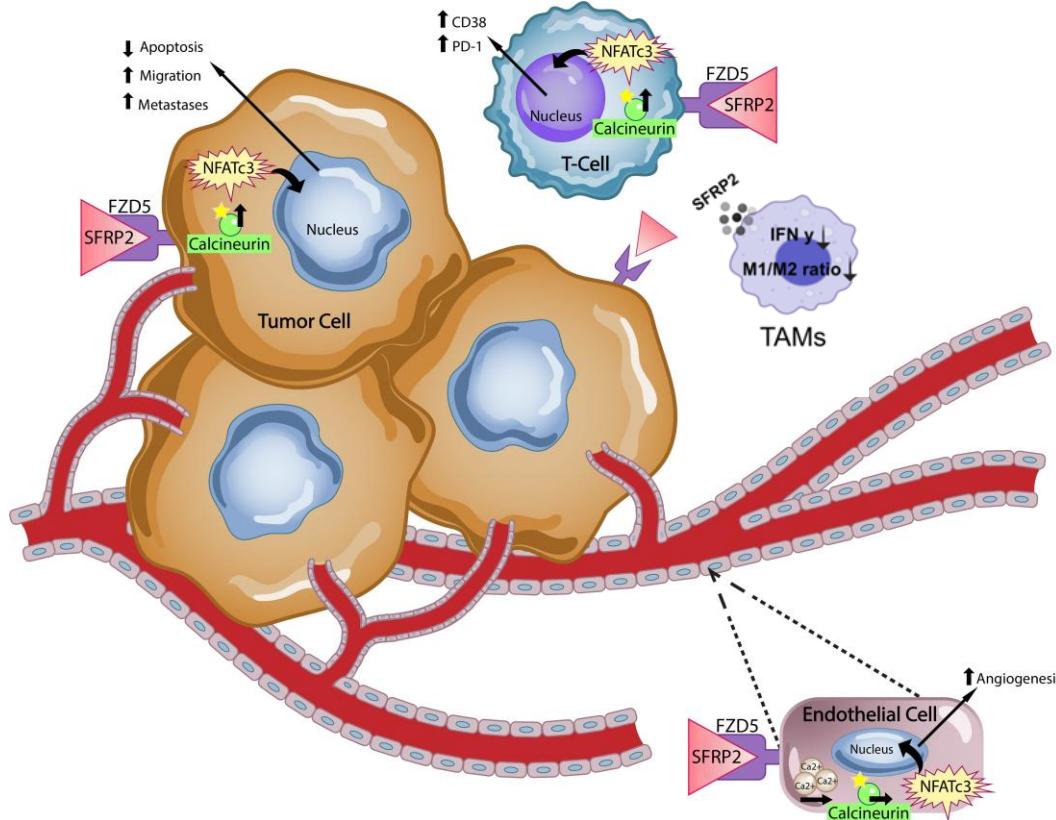
# Various Targets of Cancer Therapeutics

## Current Therapies Focus on One of the Targets



# Therapeutic Target Across Common Pathway in Tumor and Tumor Microenvironment

## SFRP2 Regulates the Non-Canonical Wnt-Signaling Cascade In Tumor Cells, Endothelial Cells, T-Cells, and Tumor Associated Macrophages (TAMs)



### IVT-8086 (humanized monoclonal antibody)

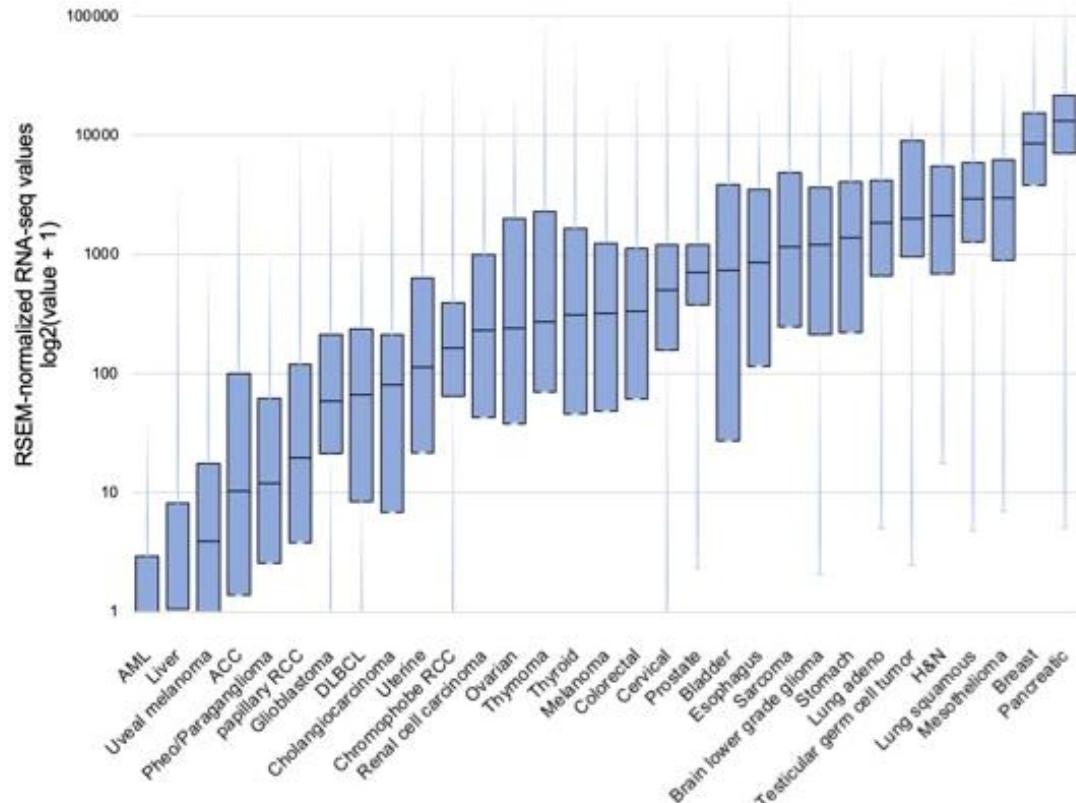
- Only therapeutic targeting SFRP2 and blocking the pathway that impacts four key cell types associated with cancer across most tumors
- No other cancer treatment impacts these 4 cell types simultaneously when cancer is present
- IVT-8086 treatment results in increased tumor apoptosis, reduces CD38 and PD-1 from TILs, increases IFN $\gamma$  in TAMs and repolarizes macrophages, and inhibits angiogenesis

#### Klauber-DeMore Lab Pubs

Bhati, R. et. al., *Am J Pathol*, 2008  
Courtwright, A. et al, *Cancer Research* , 2009  
Siamakpour-Reihani, R. et al. *Plos One*, 2011  
Fontenot, E. et. al., *Mol Cancer Ther.*, 2013  
Peterson, YK et. al., *Angiogenesis*, 2017  
Nasarre, P, et al., *Cancers* 2021

# SFRP2 is Overexpressed Across Many Tumor Types

The Cancer Genome Atlas (TCGA) SFRP2 expression in Human Tumors



Initial cancers targeted:  
Pancreatic, Breast Cancer,  
and Sarcomas including  
osteosarcoma have high  
SFRP2 RNA expression

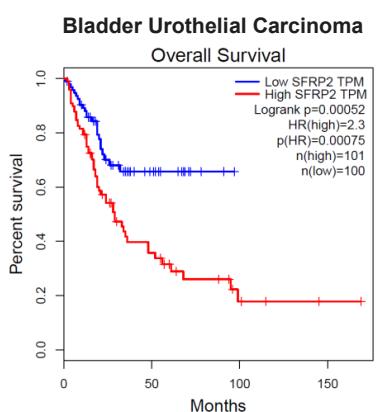
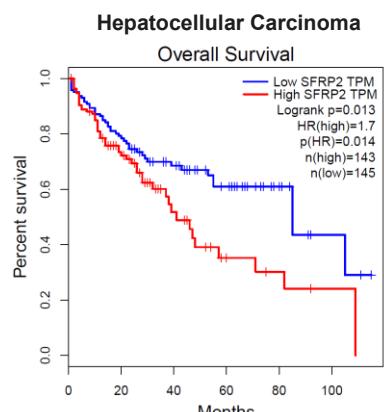
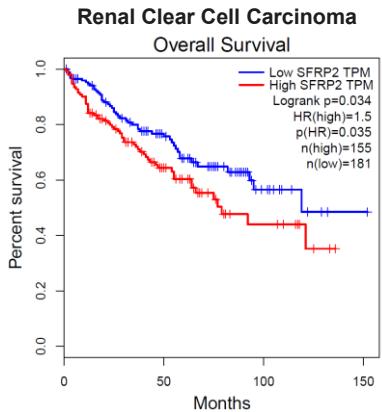
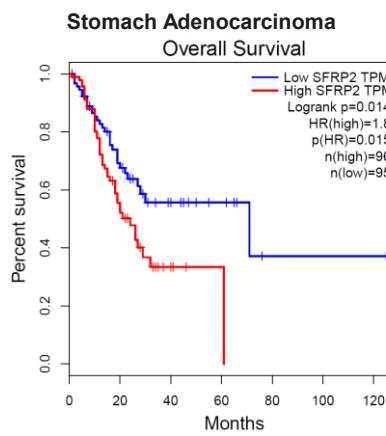
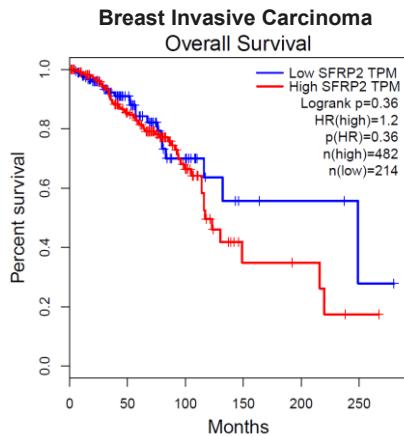
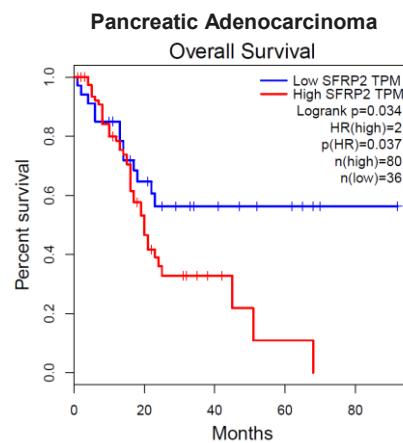
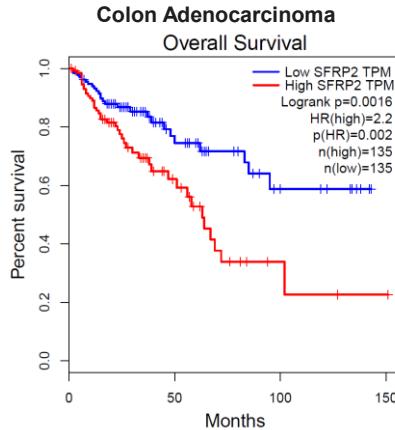
Siegel, J., Klauber-DeMore et al  
Cancer Biomarkers 2023

# SFRP2 Role in Cancer Growth and Progression Widely Validated By Other Investigators Across Various Cancers

Tumor type	Effect
Breast (triple negative)	IVT-8086 inhibits triple negative breast cancer <i>in vivo</i> ; increases apoptosis, decreases angiogenesis, decreases NFAT activation.
Angiosarcoma and Osteosarcoma	IVT-8086 inhibits angiosarcoma and osteosarcoma <i>in vivo</i> ; increases apoptosis, decreases NFAT activation
Colorectal (CRC)	Cancer-associated fibroblasts (CAFs) in colorectal cancer promote angiogenesis that favors the tumor access to nutrients and oxygen, in addition to cancer initiation and progression. Tumor stroma (which include CAFs) have been shown to secrete SFRP2 (the highest gene expressed). Patients with the poorest survival prognosis with colorectal cancer are characterized by a robust tumor stromal response.
Renal cell carcinoma	Transfection of SFRP2 in renal cell carcinoma promotes tumor growth <i>in vivo</i>
Breast	Overexpression of transfected SFRP2 in MCF7 breast cancer cells increased their resistance to apoptotic signals <i>in vitro</i> . SFRP2 overexpression <i>in vivo</i> was found to increase the metastatic burden in the lung in both human and mouse models, with a particularly pronounced increase in large metastases. SFRP2 was found to be the key regulator of breast cancer metastases to the lung.
Multiple Myeloma (MM)	RPMI8226 and U266 MM cell lines and primary MM cells suppress <i>in vitro</i> mineralization as well as alkaline phosphatase activity in osteoblasts induced by bone morphogenetic protein 2 (BMP-2). These cell lines produce, SFRP-2, but not other Wnt inhibitors including SFRP-1, SFRP-3, and dickkopf 1 (DKK-1) at the protein level. SFRP-2 suppressed osteoblast differentiation induced by BMP-2, and immunodepletion of SFRP-2 significantly restored mineralized nodule formation <i>in vitro</i> , suggesting a predominant role for MM cell-derived SFRP-2 in the impairment of bone formation by MM.
Lung cancer	Overexpression of SFRP2 promoted tumor growth in lung cancer, while silencing SFRP2 reduced lung cancer growth.
Pancreas	Adipocytes shown to induce epithelial-to-mesenchymal transition (EMT) and aggressiveness in models of pancreatic preneoplastic lesions by orchestrating a complex paracrine signaling of soluble modulators of the non-canonical WNT signaling pathway, which in turn, produces a more aggressive phenotype in models of pancreatic preneoplastic lesions.
Prostate	SFRP2 is the key factor in chemotherapy resistance in damaged tumor microenvironment in prostate cancer.
Osteosarcoma	High expression of SFRP2 was found in osteosarcoma metastases, and gain of function studies revealed stable overexpression of SFRP2 within localized human and mouse osteosarcoma cells significantly increased cell migration and invasive ability <i>in vitro</i> and enhanced metastatic potential <i>in vivo</i> .
Gastric	m1A-dependent epitranscriptomic control of SFRP2 is a novel regulator of the NFAT/TOX mediated immune evasion axis in GC. The m1A scoring system may refine patient stratification, and targeting SFRP2 represents a promising strategy to overcome ICI resistance.
Rhabdomyosarcoma	Transgenic model of rhabdomyosarcoma which with high SFRP2 expression and increased resistance to apoptosis.
Malignant glioma	SFRP2 overexpressing intracranial glioma xenografts were significantly larger than xenografts consisting of control cells in nude mice.
Melanoma	Increase of SFRP2 in older patients was determined to increase angiogenesis and metastasis, in addition to therapy resistance.

# SFRP2 mRNA Expression Levels Correlate with Survival in Cancer Patients

## Patients with lower SFRP2 levels in tumors have better survival outcome



**GEPIA** is a interactive web server for analyzing the RNA sequencing expression data of 9,736 tumors and 8,587 normal samples from the TCGA and the GTEx projects.

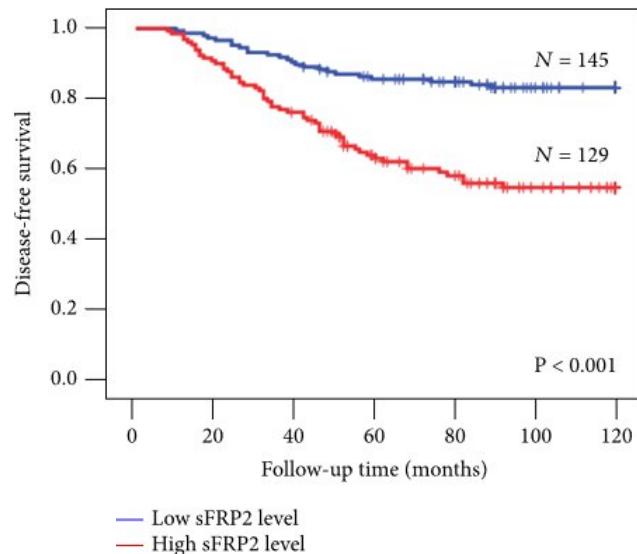
### Abbreviations

TPM – Transcripts per million  
HR – Hazard Ratio

Tang, Z. et al. (2017) GEPIA: a web server for cancer and normal gene expression profiling and interactive analyses. *Nucleic Acids Res*, 10.1093/nar/gkx247.

# SFRP2 Serum Levels Correlate with Various Tumor Assessments Including Patient Outcome Clinical Validation of Potential Diagnostic for Early Diagnosis and Reoccurrence Monitoring

- SFRP2 serum concentrations compared between 274 breast cancer patients and 147 healthy controls
- SFRP2 elevated in breast cancer patients compared to normal
- SFRP2 levels are positively associated with tumor size, lymph node metastases, TNM stage, and Ki67 rate.
- SFRP2 serum levels associated with progression free survival
- Multivariate analyses shows SFRP2 independent prognostic factor for poor prognosis



Kaplan-Meier survival curves of breast cancer patients. Progression-free survival rate of breast cancer patients with high ( $>58$  ng/mL) and low ( $\leq 58$  ng/mL) serum SFRP2 levels.

Chumei Huang, Zhuangjian Ye, Jianxin Wan, et al., "Secreted Frizzled-Related Protein 2 Is Associated with Disease Progression and Poor Prognosis in Breast Cancer," Disease Markers, vol. 2019, Article ID 6149381, 7 pages, 2019.

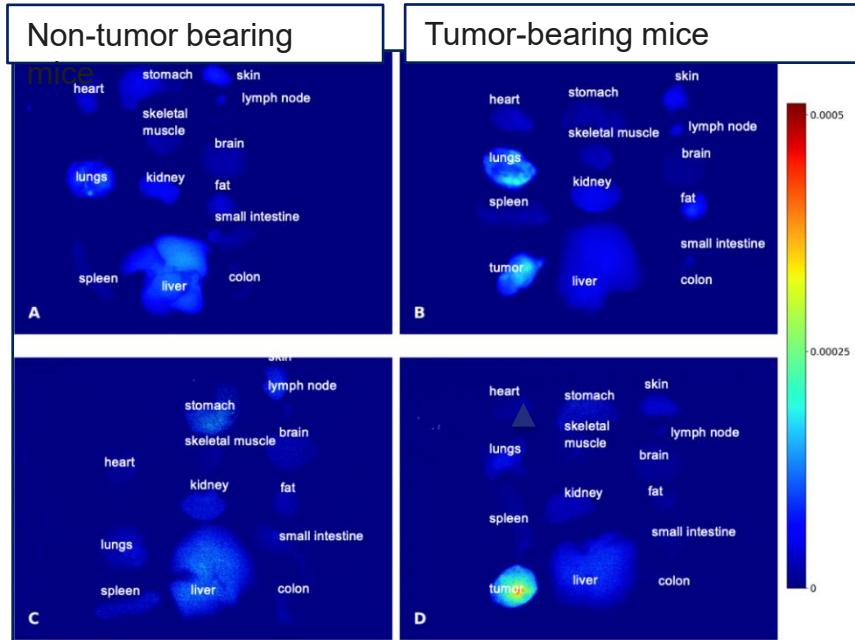
# Cancer Diagnostic in Development as a Sensitive Test for Early Cancer Screening, as a Prognostic Marker for Assessing Patient Benefit, and Marker of Reoccurrence

## *Validation Studies Across Multiple Cancers*

Tumor Type	Findings	Reference
Breast Cancer	Human serum SFRP2 prognostic for survival , elevated tumor vs normal	Huang, C. et al. Dis. Markers, 2019
Pancreatic Cancer	Human tumor SFRP2 protein and mRNA prognostic for survival, elevated tumor vs normal	Seigel, J et al Cancer Biomarkers, 2023
Osteosarcoma	Mouse serum SFRP2 elevated tumor vs normal, serum levels decrease with treatment	Nasarre, P et al, Cancers 2021
Ovarian Cancer	Human SFRP2 mRNA associated with stage	Liu, H. et al Chinese Medical Journal, 2023
Gastric Cancer	Human tumor SFRP2 mRNA associated with stage and elevated vs normal	Liu, D. et al Life, 2021

# Biodistribution: IVT-8086 Localizes to the Tumor and Not Normal Tissue

IgG1

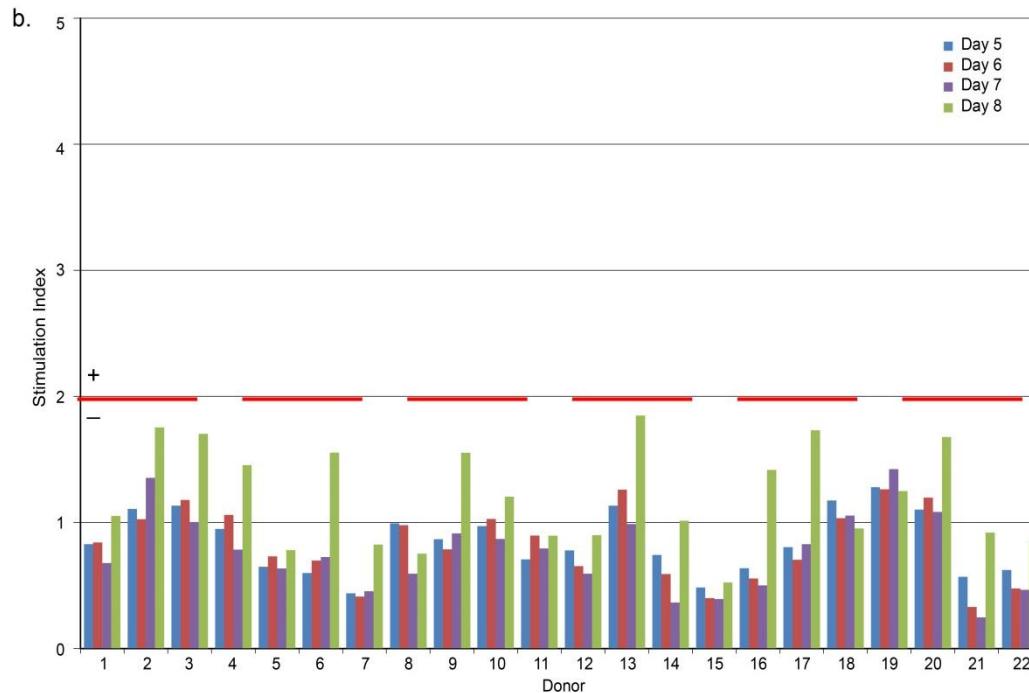


Methods: Mice were injected with 5 million MDA-MB-231 cells. Treatment of IVT 80-86 or IgG1 control iv at 4 mg/kg in 100  $\mu$ L.

The *in vivo* kinetics of IVT 8086 was measured using treatments with NIR-conjugated antibody. Organ distribution of the mAb monitored by measuring the emission of Dylight 755 over 72 hours with the *in vivo* Maestro imaging system. After the complete metabolism of the treatment, we administered another dose of NIR-tagged antibody to the mice and measured the fluorescence in organs after euthanasia and organ resection at 72 hours.

The organs extracted and imaged included tumor, liver, spleen, kidney, heart, lung, brain, stomach, small intestine, large intestine, lymph node, fat, and skeletal muscle. A NIR-tagged IgG1 control was used as a treatment control, and tumor-free mice served as healthy controls

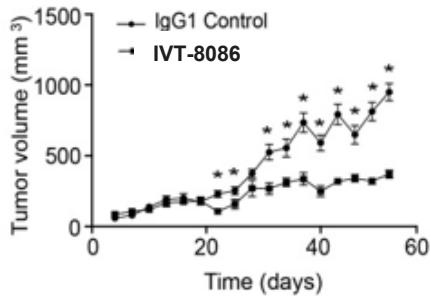
# IVT-8086 is Non-Immunogenic



Healthy donor T-cell proliferation responses to test antibodies. Peripheral blood mononuclear cell (PBMC) from bulk cultures were sampled and assessed for proliferation on days 5, 6, 7 and 8 after incubation with the three test samples. Proliferation responses with an  $SI \geq 2.0$  ( $p < 0.05$ ), indicated by red dotted line that were significant ( $p < 0.05$ ) using an unpaired, two sample student's t test were considered positive.

# IVT-8086 Significantly Reduced Tumor Growth in A Highly Chemoresistant Hs578T Triple Negative Breast Tumor *in vivo* with No Signs of Toxicity

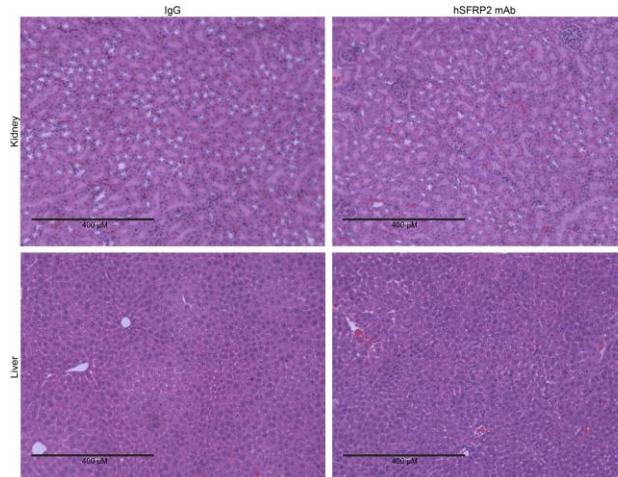
## Metaplastic Triple Negative Breast (Hs578t) CHEMORESISTANT



\*Day 0 is counted from baseline date, which is 30 days from tumor inoculation.

Nude mice with Hs587t breast cancer xenografts that were established (appr 100 mm<sup>3</sup>) were treated with hSFRP2 mAb or IgG1 control every three days beginning of Day 30.

- 61% reduction in tumor volume in the IVT-8086 treated mice (n=11, (\*P<0.05)
- No adverse clinical signs or weight loss seen over 50 days of treatment.

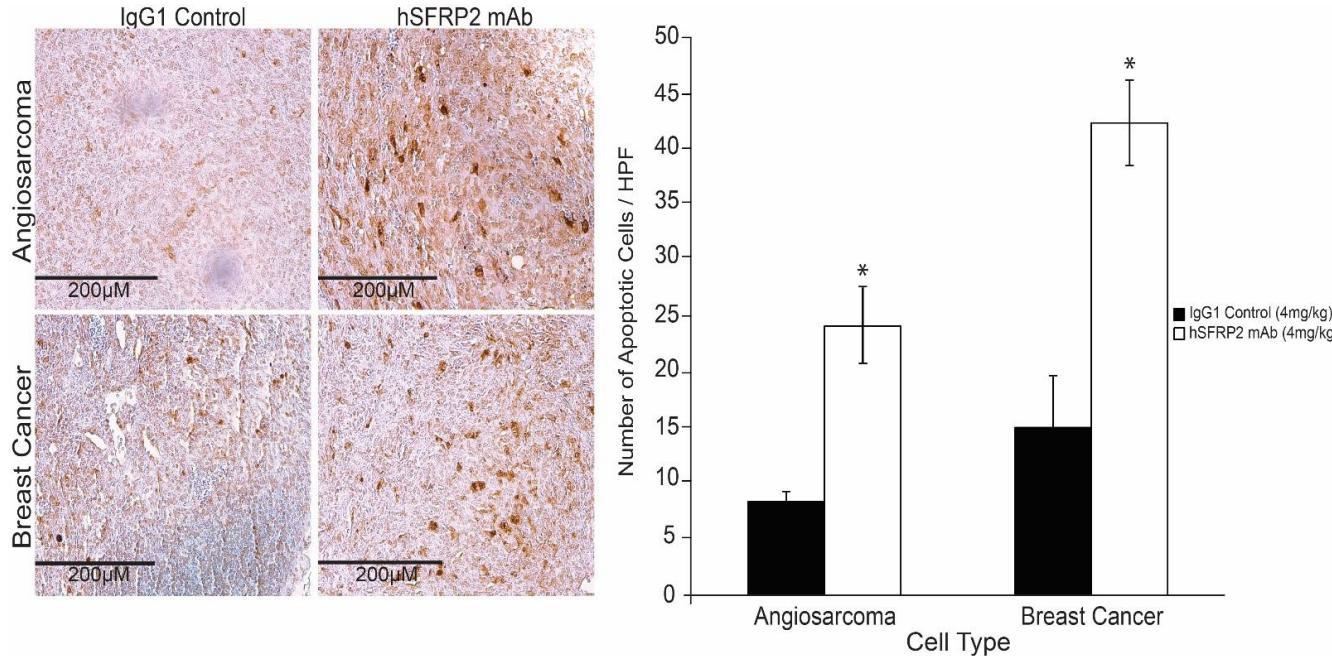


There were No Histological Changes in the Liver and Kidneys Following Multiple Dosing Administration at 4 times the Efficacious Dose (20 mg/kg) of IVT-8086 in Mice Injected with Angiosarcoma Cells

Mice injected with SVR angiosarcoma cells were treated with IVT-8086 mAb at a dose of 20 mg/kg i.v. every three days; or IgG1 control, for 21 days. Histological evaluation of kidneys and livers from all mice at 20 mg/kg dose was conducted by a board-certified pathologist.

Garcia D, et al. Ann Surg Oncol. 2019 Dec;26(13):4782-4790.

# IVT-8086 Increases *in vivo* Tumor Apoptosis



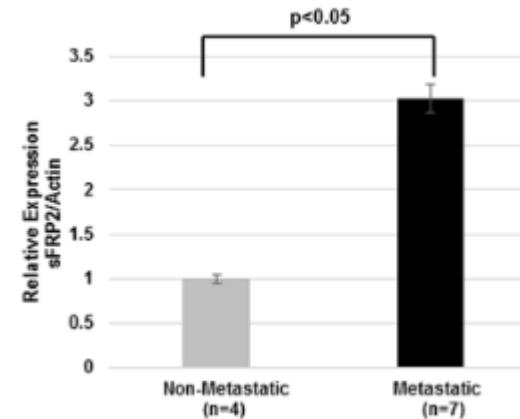
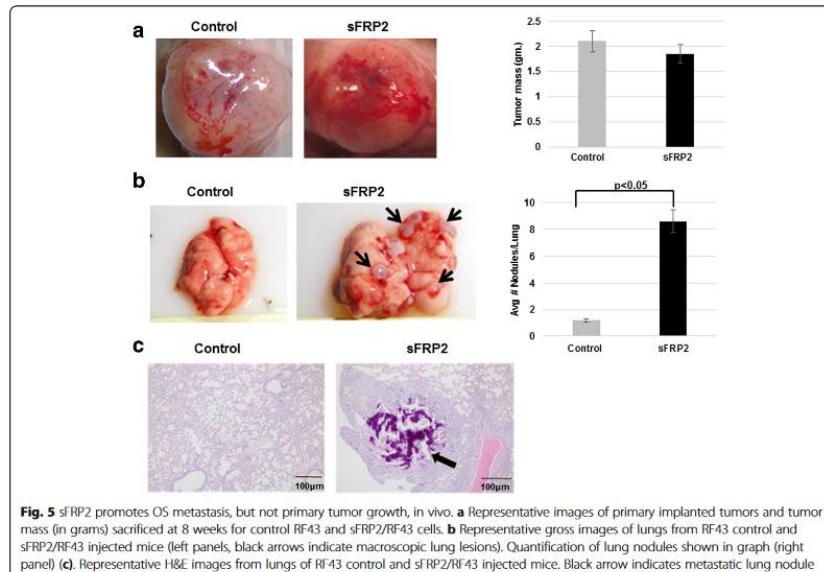
IVT-8086 promotes apoptosis in tumors. (Left) Paraffin embedded SVR angiosarcoma (upper panels) and Hs578T metaplastic breast cancer (lower panels) were sectioned and processed for TUNEL staining. The number of apoptotic cells (brown) was counted in each field. A total of 10 tumors per treatment (n=10) were used for the analysis. (Right) Bar graph showing the increase in the number of apoptotic cells in tumors treated with IVT-8086 (white bars) compared to IgG1 control treated tumors (black bars). \*:p≤0.05.

Garcia D, et al. Ann Surg Oncol. 2019 Dec;26(13):4782-4790

Non-confidential

# SFRP2 Overexpression Enhances Osteosarcoma Metastases and Correlates with Poor Survival Outcome in Patients – Clinical Validation of Target

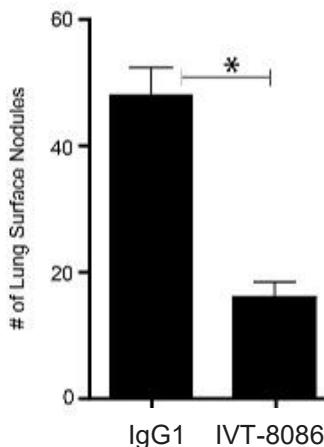
- SFRP2 within localized human and mouse OS cells significantly increased cell migration and invasive ability *in vitro* and enhanced metastatic potential *in vivo*<sup>1</sup>
- Knockdown of SFRP2 within metastatic human and mouse OS cells demonstrated decreased cell migration and invasion ability *in vitro*<sup>1</sup>
- Strong SFRP2 expression in OS patient samples correlates with poor survival<sup>2</sup>
- SFRP2 overexpression suppresses normal osteoblast differentiation, promotes OS features, and facilitates angiogenesis via autocrine and paracrine mechanisms<sup>2</sup>



qPCR analysis comparing expression of SFRP2 in metastatic primary human osteosarcoma tumor tissue to non-metastatic tumor

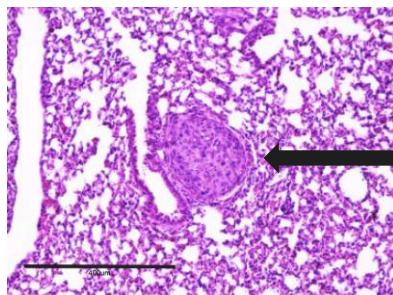
1. Techavichit P, et al. *BMC Cancer*. 2016 Nov 8;16(1):869.
2. Kim H, et al. *Proc Natl Acad Sci U S A*. 2018;115(4):

# IVT-8086 Reduces Established Metastatic Osteosarcoma in Mouse GEMM Model as Monotherapy and Reduces CD38 in T-Cells

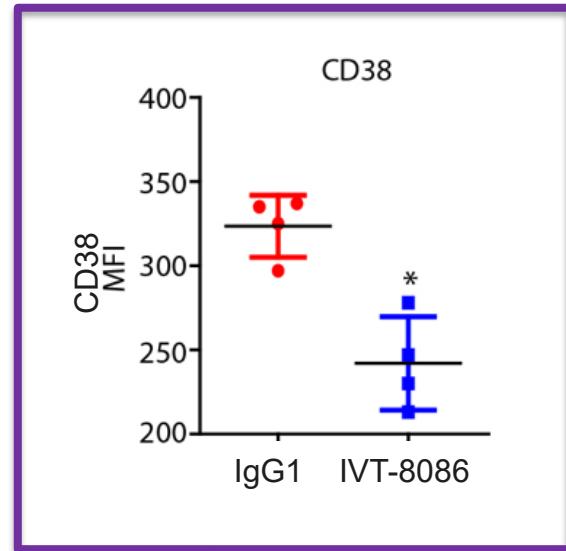


Osteosarcoma RF420 cells from a **Osteosarcoma GEMM model** were injected intravenously in C57BL6 mice. Treatments with an IgG1 control or IVT-8086 (4 mg/kg iv every 3 days), starting 10 days after the injection of tumor cells when lung mets were established. Three weeks later, the animals were euthanized, their lungs were resected, and surface nodules were counted

\*p≤0.0001; n=12. Representative lungs with tumor



Histological confirmation of established lung mets by Day 7



\*p≤0.02

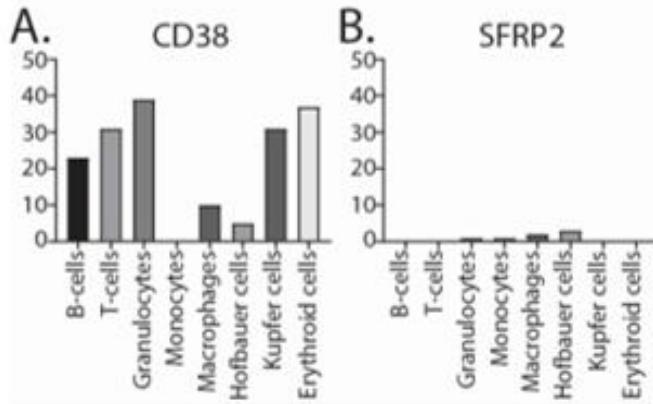
Nasarre, P. et al. Overcoming PD-1 Inhibitor Resistance with a Monoclonal Antibody to Secreted Frizzled- Related Protein 2 in Metastatic Osteosarcoma. *Cancers* 2021, 13, 2696.

## CD38 Overexpression has been Implicated as Being Responsible for Resistance to Checkpoint Inhibitors in Some Tumors

- One recently reported mechanism of resistance to checkpoint inhibitors in other cancer is through the up regulation of CD38, which regulates NAD+.
- Intracellular NAD+ levels have a profound influence on diverse signaling and metabolic pathways of T cells, and hence dictate their functional fate.
- Overall, the CD38- NAD+ axis is crucial in altering T-cell response in various pathophysiological conditions.
- Chen et al demonstrated that CD38 upregulation in tumors induces resistance to PD-1/PD-L1 blocking antibodies and co-inhibition of CD38 and PD-L1 improves antitumor immune response\*.

*Chen, L. Cancer Discovery, 2018*

# Resistance to PD-1 Inhibitors Has Been Shown to be Associated with Increased CD38 Expression in T-Cells<sup>1</sup>



CD38 is ubiquitously expressed on most cells, including normal hematopoietic cells

- Darzalex is an approved CD38 mAb for multiple myeloma (MM) which binds directly to CD38 wherever it's expressed
- Unacceptable toxicity in combination with PD-1 inhibitors in clinical trials, all trials terminated

SFRP2 is selectively expressed only in the tumor microenvironment and not in normal hematopoietic cells

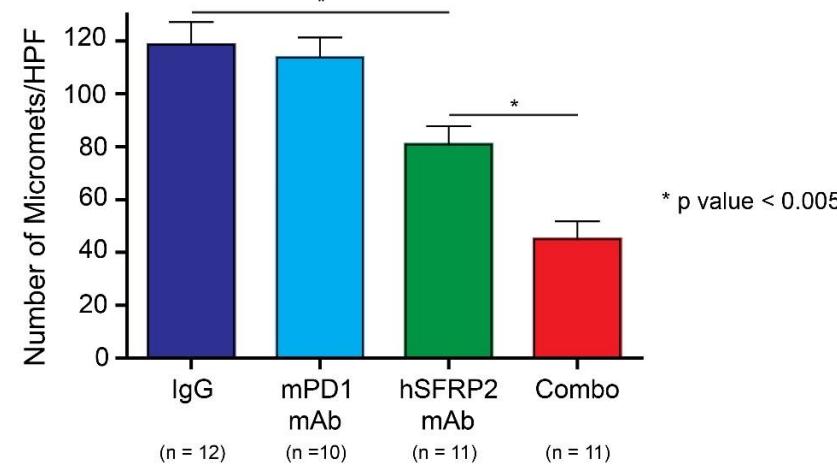
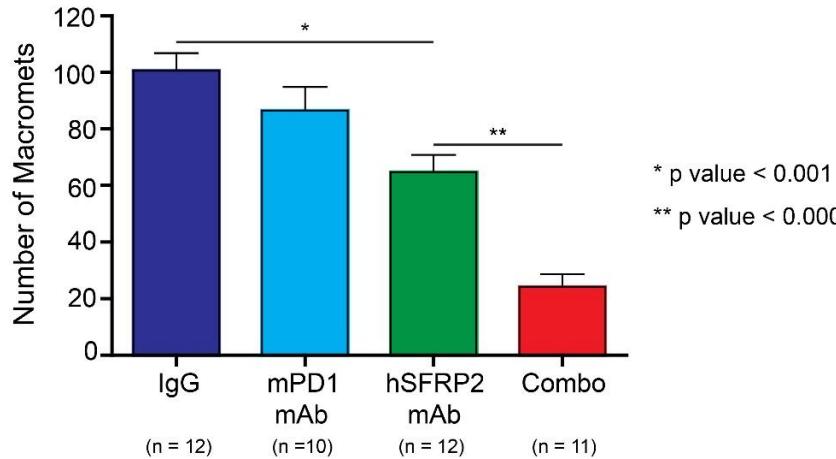
- **IVT-8086 administration associated with selective decreased CD38 expression in T-Cells, with no impact on CD38 on normal tissue or blood cells**
- **Rescues T-Cell exhaustion**

Targeting SFRP2 will specifically inhibit CD38 only in cells that express SFRP2, which is restricted to the tumor and tumor microenvironment

- IVT-8086, by antagonizing SFRP2, has been shown to improve efficacy of PD-1 inhibitors in combination without off target toxicity
- **This pattern of improved efficacy of IVT-8086 in combination with PD-1 inhibitors should occur across most other cancers**

1. Chatterjee S, et. al., *Cell Metab* 2018,  
Philip M, et al, *Nature* 2017

# IVT-8086 in Combination with a PD-1 mAb is Synergistic at Inhibiting Metastatic Osteosarcoma in GEMM Osteosarcoma Cell Line Model (RF420)

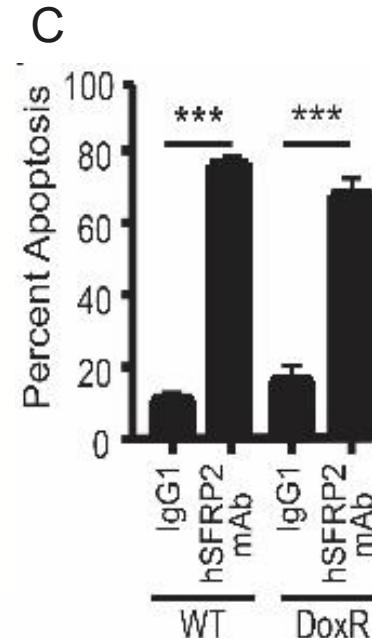
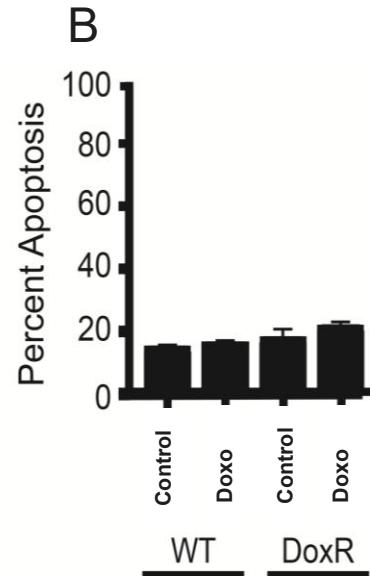
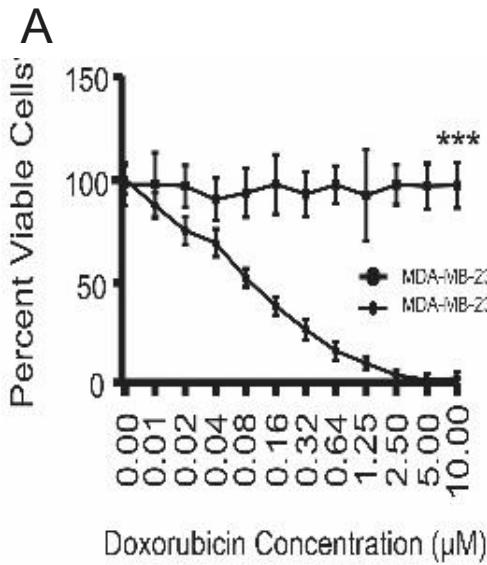


RF420 mouse osteosarcoma cells were injected in the tail vein of C57BL/6 mice. Starting on day 7 mice were treated with either IgG1 control (Xolair) 4 mg/kg iv weekly, or mouse PD-1 ab (200ug/mouse) every 3 days, or IVT-8086 4 mg/kg iv every 3 days, or the combination of both antibodies every 3 days for 21 days. .

Nasarre, P. et al. Overcoming PD-1 Inhibitor Resistance with a Monoclonal Antibody to Secreted Frizzled- Related Protein 2 in Metastatic Osteosarcoma Cancers 2021, 13, 2696.

Non-confidential

# IVT- 8086 Induces Tumor Apoptosis in TNBC Cells Resistant to Doxorubicin (DoxR)



- A. MDA-MB-231 breast cancer wild-type (WT) cells cultured with Dox for one year to create a Dox-resistant cell line (DoxR).
- B. Dox does not affect apoptosis in WT or DoxR cells.
- C. DoxR cells remained sensitive to IVT-8086 at inducing apoptosis

# IVT 8086 Inhibits Metastatic TNBC and Increases Tumor Apoptosis

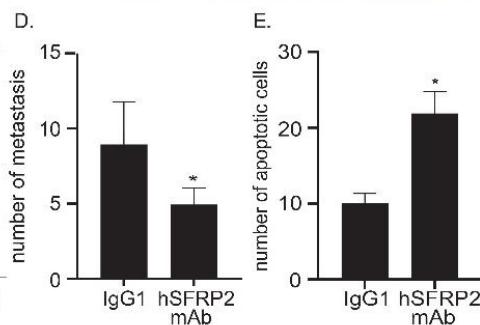
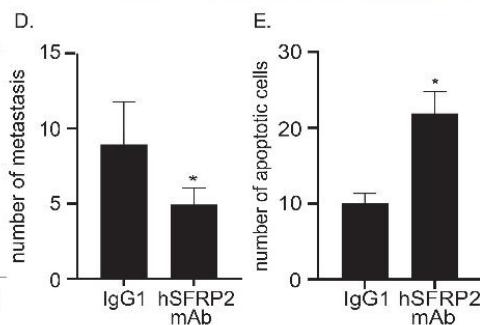
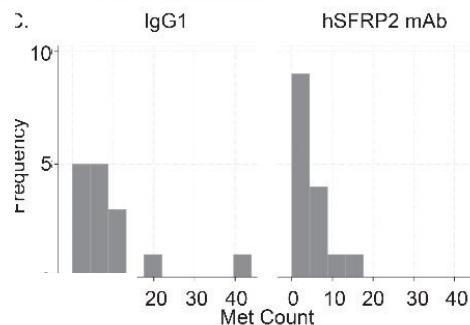
A.

IgG1



B.

hSFRP2 mAb



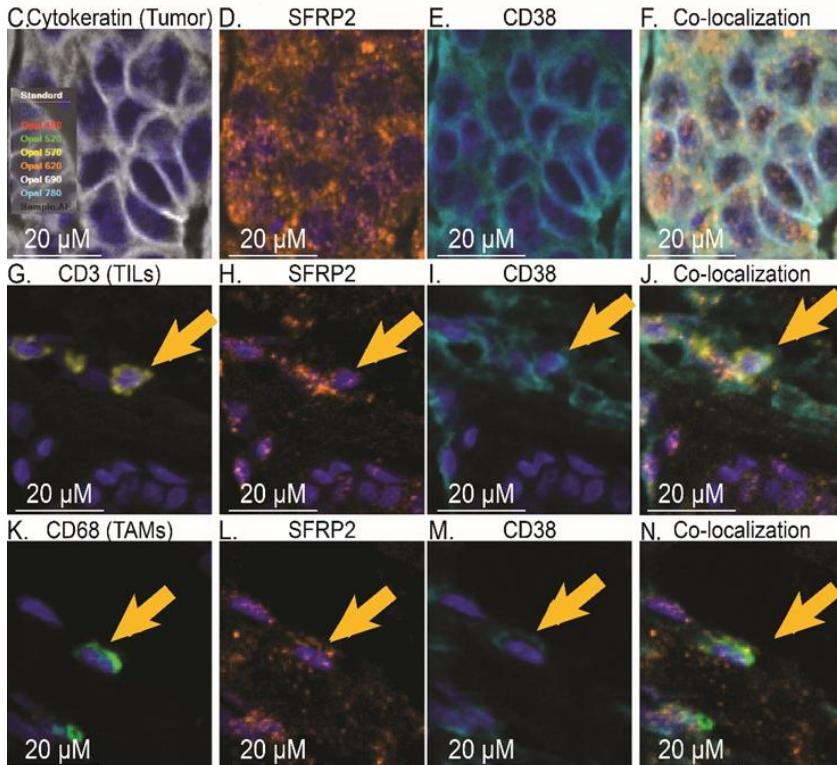
C57BL6 mice injected via tail vein with E1077 murine TNBC. Treated with control of IVT 80-86. After 3 weeks Lungs resected and mets counted (A-D), showing a reduction in lung mets.

E). Tunnel assay on lung mets show an increase in apoptosis in tumors treated with IVT 80-86

# SFRP2 and CD38 are Highly Expressed in Tumor Cells, Tumor Infiltrating Lymphocytes (TILs) and Tumor Associated Macrophages (TAMs)

A.	SFRP2	Mean±SEM
% Tumor Cells SFRP2 +	87.57±8.11	
% TAMs SFRP2 +	90.34±5.59	
% TILs SFRP2 +	96.38±2.21	

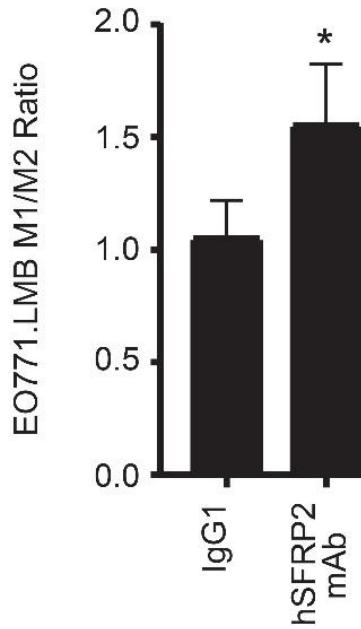
B.	CD38	Mean±SEM
% Tumor Cells CD38 +	39.75±20.17	
% TAMs CD38 +	43.16±14.94	
% TILs CD38 +	43.36±9.05	



Four human TNBC tumors underwent multiplex IHC staining with antibodies to SFRP2, CD68, CD38, CytoKeratin, and CD3. (A) InForm spatial analysis showed a high degree of cells in the tumor, TAMs and TILs staining positive for SFRP2. (B) Similarly, a high degree of cells in the tumor, TAMs and TILs stained positive for CD38. (C) A human TNBC tumor stains positive for CytoKeratin, shown in white. (D) SFRP2, in orange (E) CD38 in teal. (F) colocalization of CytoKeratin, SFRP2, and CD38. (G) The same tumor also stains positive for CD3, shown in yellow, (H) SFRP2, in orange, (I) CD38, in teal, (J) and colocalization of CD3, SFRP2, and CD38. (K) Lastly, the tumor stains positive for CD68 are shown in green, (L) SFRP2, orange, (M) CD38, teal, and (N) colocalization of CD68, SFRP2, and CD38.

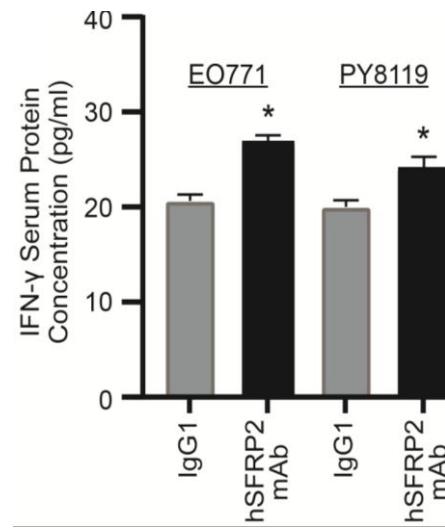
# Changes in Tissue M1/M2 Ratio and Serum Interferon Gamma (IFN- $\gamma$ ) in IVT-8086 Treated TNBC Mets

## Increase in M1/M2 TAM Ratio in Lung Mets Treated with IVT-8086



FFPE E0771 lung slices were stained with antibodies to CD86, CD163, and F4/80. M1/M2 ratios for hSFRP2 mAb treated mice were increased compared to IgG1 treated mice (\* $p=0.028$ , n=3)

## Increase in Serum IFN- $\gamma$ in Mice with Breast Cancer Lung Mets Treated with IVT-8086



Serum from IgG1 and IVT-8086 treated mice subjected to ELISA for IFN- $\gamma$ . There was an increase of IFN- $\gamma$  protein in the serum of EO771 TNBC ( $p<0.0001$  n=5) and PY8119 TNBC ( $p<0.0001$  n=7) tumor-bearing mice following treatment with IVT-8086.

# SFRP2 Impact in TNBC and Mechanistic Role of IVT-8086

- SFRP2 is expressed in a high percentage of patients with TNBC
- SFRP2 localizes to the tumor immune microenvironment
- Antagonizing SFRP2 will inhibit the growth of metastatic TNBC
- A mechanistic rationale for IVT-8086: increasing interferon gamma (IFN- $\gamma$ ) secretion in TAMs resulting in increased M1/M2 ratio
- IVT-8086 increases apoptosis in doxorubicin-resistant TNBC

# SFRP2 Expressing Cancer-Associated Fibroblasts (CAFs) Impact Stroma Resulting in Poor Patient Survival

- **Cancer-associated fibroblasts (CAFs)** are one of the most prominent cell populations in the tumor microenvironment (TME).
- Cancer-associated fibroblasts (CAFs) have multiple tumor-promoting functions in drug resistance, regulation of the niche of cancer stem cells and formation of the immunosuppressive network.
- In a recent publication an aggressive subpopulation of SFRP2 expressing CAFs (designated as SFRP2\_CAFs) was found to be consistently present in primary and metastatic lesions in patients with advanced head and neck squamous cell carcinoma (HNSCC) impacting the stroma and was associated with poor survival outcome in these patients.<sup>1</sup> Similar findings were found in patients with high grade appendiceal cancers and was also associated with poor survival.

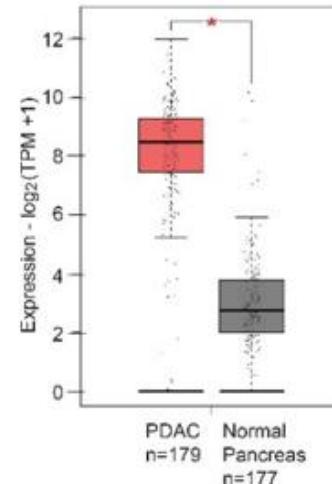
1. Wang, Q., Zhao, Y., Tan, G. et al. Single cell analysis revealed SFRP2 cancer associated fibroblasts drive tumorigenesis in head and neck squamous cell carcinoma. *npj Precis. Onc.* **8**, 228 (2024). <https://doi.org/10.1038/s41698-024-00716-5>

# Background on KRAS and Pancreatic Ductal Adenocarcinoma (PDAC)

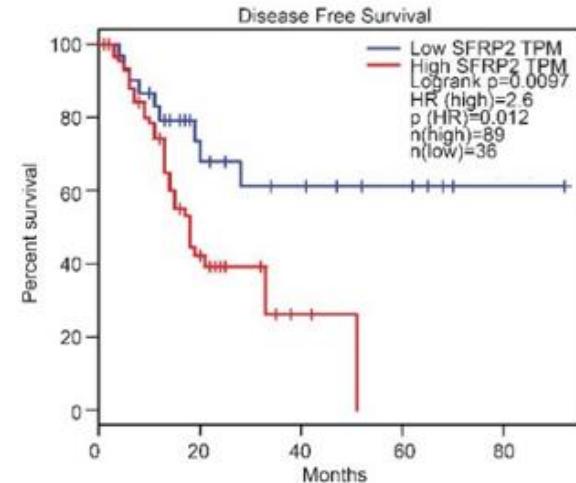
- Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal solid malignancies with increasing incidence.
  - The poor prognosis is due to the aggressive nature of the tumor, late detection, and the resistance to chemotherapy and radiotherapy.
  - The majority of patients (80-85%) at first diagnosis are locally advanced or metastatic disease and just 15-20% patients are diagnosed in an early stage
- PDAC is the fourth leading cause of cancer deaths in the United States
- The major genetic event in PDAC is the activating point mutation of the KRAS oncogene
  - **KRAS is mutated in 90% of patients with PDAC**
- KRAS mutation activates the KRAS protein which contributes to cancer cell proliferation, metabolic reprogramming, immune escape, and therapy resistance in PDAC, acting as a critical driver of the disease.
  - KRAS mutation is positively associated with poorer prognosis in pancreatic cancer patients.
  - The **G12D mutation** is the most common in pancreatic cancer, present in approximately 35% of people diagnosed with the disease.

# SFRP2 is Elevated in Pancreatic Ductal Adenocarcinoma (PDAC) and Prognostic for Survival using TCGA

- Using The Cancer Genome Atlas (TCGA) data set of 179 patients with PDAC, SFRP2 mRNA was found to be highly expressed compared to normal pancreas



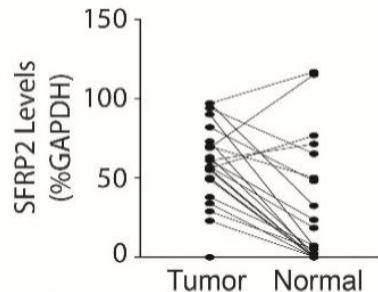
- In patients with PDAC, high SFRP2 expression was associated with worse disease-free survival (DFS) compared to patients with low SFRP2 levels.



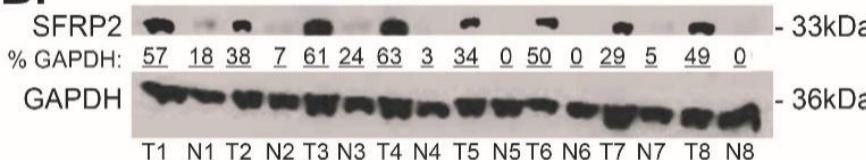
# SFRP2 Protein Increased in PDAC and Not in Adjacent Normal Tissue

## SFRP2 is an Independent Prognostic Factor for Poor Prognosis

A.



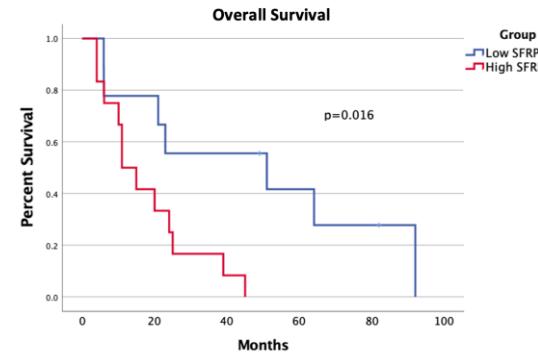
B.



(A) Western blot comparing the levels of SFRP2 between tumor tissue from patients and their normal adjacent pancreatic tissue.

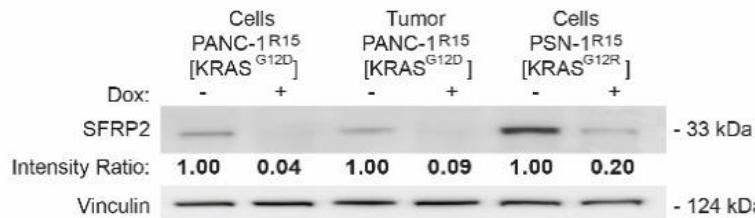
(B) Representative western blot of tumor tissues (T) and their normal adjacent tissues (N).

- In patients with Stage 1 and Stage 2 PDAC cancer undergoing pancreatic resection at Medical University of South Carolina (MUSC), SFRP2 protein was elevated compared to adjacent normal tissue.
- SFRP2 levels in tumors even in early stage PDAC correlated with outcome



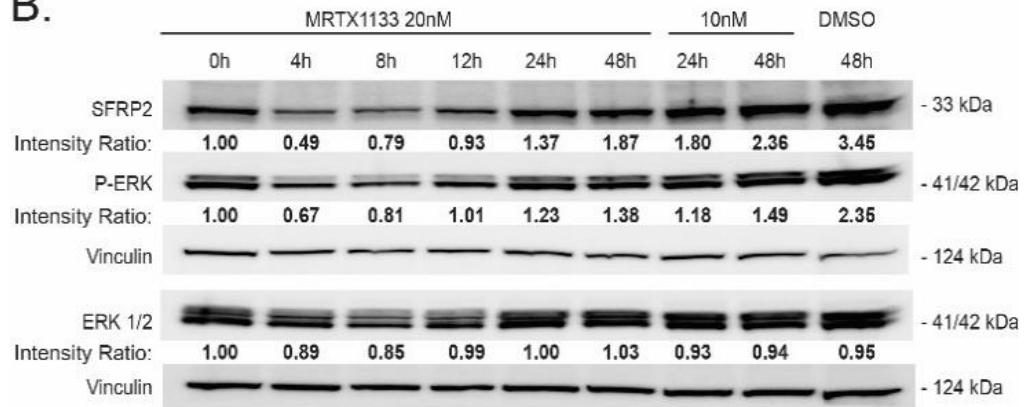
# KRAS Demonstrated to Regulate SFRP2 in vitro and in vivo

A.



(A) Western blot of PDAC expressing a doxycycline (DOX)-inducible CFP-R15 monobody (KRAS inhibitor). DOX-induced R15 (+) reduced SFRP2 levels in both PDAC cells *in vitro* and a PANC-1 tumor *in vivo*. DOX: doxycycline.

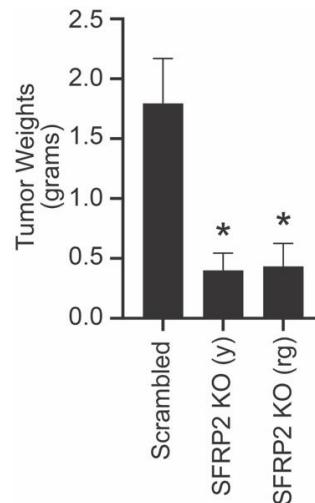
B.



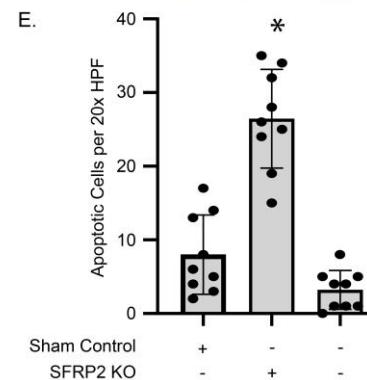
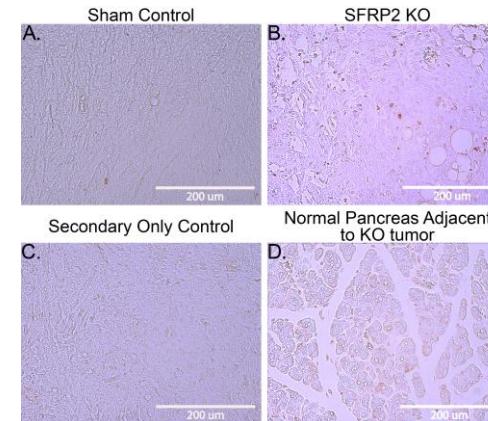
(B) Western blot analysis of PANC-1 cells treated with DMSO or MRTX1133 (10 or 20 nM), a noncovalent selective KRAS<sup>G12D</sup> inhibitor, for various periods of time shows a reduction of P-ERK and SFRP2 at 4 hours compared to control.

- Two different KRAS inhibitors inhibited SFRP2 protein production, including one targeting G12D which is the most common KRAS mutation in PDAC
- SFRP2 was shown to be regulated by KRAS in PDAC

# SFRP2 KO Tumors have Reduced Growth in an Orthotopic PDAC Model *in vivo*



$n = 6$  mice per group;  $p < 0.05$  by one-way ANOVA.



# Clinical Development Plan Rationale for IVT-8086 Initially Focused on Four Cancers, Sarcoma (including Osteosarcoma), Triple Negative Breast, Multiple Myeloma, and Pancreatic Cancer

## Osteosarcoma (OS), Other Sarcomas

- Monotherapy treatment significantly reduced Lung Surface Nodules in OS ( $p \leq 0.0001$ )
- IVT-8086 in combination with a PD-1 mAb was synergistic at inhibiting lung metastases in multiple osteosarcoma GEMM Models ( $p < 0.005$ )
- Significant reduction in tumor growth in angiosarcoma tumor model compared to control group. ( $p < 0.05$ )
- Strong SFRP2 expression in OS patients correlates with poor long-term survival

## Breast Cancer Including Triple Negative Breast Cancer (TNBC)

- SFRP2 highly expressed in all human breast cancer subtypes, including TNBC
- In vivo inhibition in tumor growth in chemo-resistant triple negative breast cancer in nude mice
- SFRP2 levels in serum levels in patients across all types of breast cancer was shown to be an independent prognostic factor for poor prognosis. Kaplan-Meier curves showed a significant association of serum SFRP2 with progression-free survival
- Antagonizing SFRP2 will inhibit the growth of metastatic TNBC. A mechanistic rationale for IVT-8086: increasing interferon gamma (IFN- $\gamma$ ) secretion in TAMs resulting in increased M1/M2 ratio
- IVT-8086 increases apoptosis in doxorubicin-resistant TNBC

## Pancreatic Cancer

- SFRP2 highly expressed in pancreatic cancer, protein levels correlation with patient survival
- KRAS mutation responsible for overexpression of SFRP2 in PDAC
- SFRP2 KO tumors have reduced growth in an orthotopic PDAC model
- Adipocytes shown to induce epithelial-to-mesenchymal transition (EMT) and aggressiveness in models of pancreatic preneoplastic lesions by orchestrating a complex paracrine signalling of soluble modulators of the **non-canonical WNT signalling pathway**, which in turn, produces a more aggressive phenotype in models of pancreatic preneoplastic lesions.

## Multiple Myeloma (MM)

- SFRP2 impacts CD-38 overexpression in MM, and reduction of CD38 demonstrated to be efficacious in MM
- Primary MM cells suppress in vitro mineralization in osteoblasts induced by bone morphogenetic protein 2 (BMP-2). Immunodepletion of SFRP-2 significantly restored mineralized nodule formation, suggesting a predominant role of SFRP-2 in the impairment of bone formation in MM.
- Impacting CD-38 with IVT-8086 selective to CD-38 overexpressed in dysfunctional T-Cells, with no impact on CD-38 expressed on normal blood cells and tissues

# Tremendous Commercial Opportunity as a Monotherapy and in Combination with Checkpoint Therapy (e.g. PD-1 Inhibitors)

## PD-1 / PD-L1 Inhibitor Market: (current market size approx. \$50B)

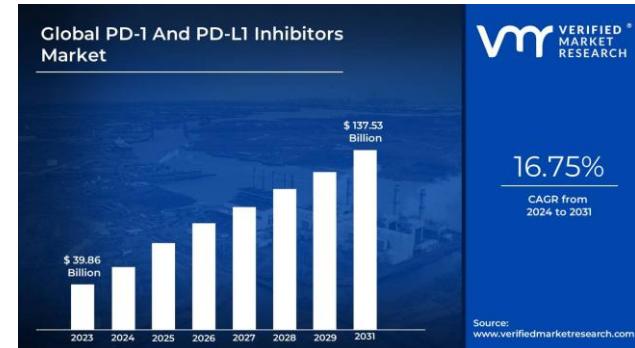
- PD-1 inhibitors are the most commonly used cancer therapeutics, and are approved for treating over 20 types of cancer. The global market for PD-1 and PD-L1 inhibitors is expected to reach \$137 billion by 2031.
- Primary and acquired resistance to PD-1 Inhibitors has been shown to be associated with CD-38 overexpression in T-Cells. The pathway that causes the over expression of CD-38 has been shown to be blocked by IVT-8086, resulting in downregulation of CD-38.
- Combination therapy of IVT-8086 with PD-1 inhibitors will dramatically benefit patients across multiple cancers by increased efficacy.
- There is a tremendous commercial opportunity for usage of IVT-8086 in combination with PD-1 inhibitors.

Sources:

PD-1 And PD-L1 Inhibitors Market By Type (PD-1, PD-L1), By Application (Hodgkin Lymphoma, Kidney Cancer, Melanoma, Non-small Cell Lung Cancer), By Distribution Channel (Hospitals, Retail Pharmacies, Online Pharmacies), & Region for 2024–2031

Report ID: 11130 | Published Date: Mar 2024 | No. of Pages: 202 | Base Year for Estimate: 2023 In-Depth Industry Outlook: PD-1 And PD-L1 Inhibitors Market Size, Forecast

[https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/iqvia\\_in-the-eye-of-the-storm\\_pd-1-inhibitors-weathering-turbulence\\_05-22-forweb.pdf](https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/iqvia_in-the-eye-of-the-storm_pd-1-inhibitors-weathering-turbulence_05-22-forweb.pdf); <https://www.mordorintelligence.com/industry-reports/pd1-and-pdl1-inhibitors-market>



## Monoclonal Antibody (mAb) Market: (current market size approx. \$180B)

- According to the World Health Organization (WHO), in 2020, around 10 million people died due to cancer globally. The monoclonal antibodies market has seen substantial growth due to the increased need for effective and affordable therapies for cancer treatment. By 2030, this market is estimated to reach >\$520 billion.
- IVT-8086 is unique to other monoclonal antibodies in that it blocks a pathway common in most cancers and impacts three key cell types associated with cancer. No other monoclonal antibody approved or in development has these broad characteristics across various cancers.

Sources:

[https://www.gminsights.com/industry-analysis/monoclonal-antibodies-market?gclid=EAIaIQobChM1v-4mMSM-Q1V-ciUCR3M8wT-EAAYAiAAEgISv\\_D\\_BwE](https://www.gminsights.com/industry-analysis/monoclonal-antibodies-market?gclid=EAIaIQobChM1v-4mMSM-Q1V-ciUCR3M8wT-EAAYAiAAEgISv_D_BwE)  
<https://www.globenewswire.com/en/news-release/2022/05/23/2448585/0/en/Monoclonal-Antibodies-Market-Size-to-Hit-US-524-68-Bn-By-2030.html#:~:text=The%20global%20monoclonal%20antibodies%20market,12.8%25%20from%202020%20to%202030>  
<https://www.prnewswire.com/news-releases/cancer-monoclonal-antibodies-market-worth-159-7-billion-by-2030-grand-view-research-inc-301589238.html>

# Tremendous Commercial Opportunity as a Monotherapy and in Combination with Checkpoint Therapy (e.g. PD-1 Inhibitors)

## Breast Cancer Market (current market size approx. \$25B)

- Breast cancer accounted for 684,996 mortalities globally in 2020. Triple negative breast cancer (TNBC) is distinct from other types of invasive breast cancer in that it grows and spreads more quickly, has fewer treatment options, and has a poor prognosis. Triple negative breast cancer accounts for about 15-20 percent of all breast cancers.
- **IVT-8086 demonstrated significant tumor shrinkage in multiple TNBC tumor models, including one model that was chemoresistant.** In addition, **SFRP2 found to be overexpressed across all types of breast cancer**, indicating the broad therapeutic treatment opportunity of IVT-8086 across all types of breast cancer.

Source: <https://www.gminsights.com/industry-analysis/breast-cancer-therapeutics-market#:~:text=Breast%20Cancer%20Therapeutics%20Market%20size%20exceeded%20USD%2025.5%20billion%20in,stimulating%20the%20overall%20market%20growth>

## Multiple Myeloma Market: (current market size approx. \$24B)

- The global multiple myeloma market is expected to reach \$39 billion by 2029. In the next 20 years, the number of cases diagnosed is expected to nearly double.
- CD38 is ubiquitously expressed on most cells, including normal hematopoietic cells. Darzalex is an approved CD38 mAb for multiple myeloma (MM) (net sales \$6B) which binds directly to CD38 wherever it is expressed and has significant off-target hematological toxicity.
- **IVT-8086 selectively impacts CD38 in tumors and T-Cells and not on normal tissues or hematopoietic cells, resulting in selective blockage of CD38 without off target toxicity.**

Source: <https://www.databridgemarketresearch.com/reports/global-multiple-myeloma-market>

## Pancreatic Cancer Market: (current market size approx. \$3.7B)

- The global pancreatic cancer market in 2021 reached \$3.7 billion and is estimated to reach \$5.6 billion by 2027. Pancreatic cancer is expected to be the second deadliest cause of cancer by 2030. Among patients with metastatic disease, the 5-year survival rate is only 2%, with median survival with treatment by existing therapies ranging from only approximately 5.5 to 8.5 months.
- **Lower SFRP2 protein levels in pancreatic tumors have been shown to correlate with better survival in pancreatic cancer patients. IVT-8086 has been shown to lower SFRP2 levels in addition to reducing tumor volume.**

Source: <https://www.mordorintelligence.com/industry-reports/pancreatic-cancer-therapeutics-diagnostics-market#:~:text=Market%20Overview,7.43%25%20from%202022%20to%202027>

## Sarcoma Market: (current market size > \$1B)

- The global sarcoma drugs market size is expected to grow at a CAGR of 8.5%. Sarcomas represent a heterogeneous group of over 50 different histological subtypes, the two major subtypes are soft tissue sarcomas (STS) and bone sarcoma (i.e., osteosarcoma). Osteosarcoma (OS) is a type of malignant bone cancer that mostly occurs in teenagers, young adults, and older adult population. Treatment options for this cancer are very limited, with no new therapy has been approved since 1991.
- **Osteosarcoma is an orphan disease and has an accelerated development pathway and would qualify for a rare pediatric voucher (cash value \$100-300M).** The market projection alone for OS is projected as \$800M/yr by 2025.

Sources: <https://www.grandviewresearch.com/press-release/global-sarcoma-drugs-market#:~:text=%7C%20CAGR%3A%208.5%25>

<https://www.grandviewresearch.com/press-release/global-sarcoma-drugs-market#:~:text=%7C%20CAGR%3A%208.5%25&text=The%20global%20sarcoma%20drugs%20market,8.5%25%20during%20the%20forecast%20period>

<https://www.prnewswire.com/news-releases/bone-cancer-drugs-market-to-grow-by-usd-996-69-million-strong-prevalence-of-osteosarcoma-in-younger-patients-will-be-one-of-the-key-drivers-technavio-301358210.html>

# Broad Patent Coverage and Data/Market Exclusivity

- **Novel Targets for Regulation of Angiogenesis** - Composition of Matter
  - Issued: U.S. Patent No. 8,734,789 (05/27/2014)
  - Issued: U.S. Patent No. 9,073,982 (07/07/2015)
- **Combination therapy of a humanized antibody to secreted frizzled related 2 with PD-1 inhibition for the treatment of cancer**
  - Filed: U.S. Provisional App. No. 62/737,155 (9/27/2018); PCT filed 2019, National filings 2021
- **Compositions and methods comprising SFRP2 antagonists**
  - Filed: U.S. and PCT applications filed 2021
  - Multiple countries granted including US
    - Global patent protection through 2042 (up to 2047 in US with extensions)

## Additional Patents filed for global protection (US and PCT):

- A Humanized Monoclonal Antibody to SFRP2 for Tumor Associated Macrophage Reduction and Polarization in Cancer
- Composition for Modulating the KRAS Pathway and Methods of Use Thereof

## Regulatory Data Exclusivity for Major Markets Post Approval for Biologics

- US – According to the Biologics Price Competition and Innovation Act of 2009 (BPCIA) **market exclusivity** until 12 years after the date of first licensure of the reference product.
- EU – 8 year period of data protection, 10 year period of marketing protection both of which can be extended 1 year to a maximum of 9 and 11 years, respectively, if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications. For orphan indications an additional 2 years of market exclusivity for completion of the pediatric investigation plan (PIP)
- Japan - Drugs containing new active ingredient - 8 years, Orphan drug 10 years

# Key Benefits of Innova Therapeutics Novel Cancer Therapeutic Platform

## Monoclonal Antibody (mAb) Platform Selectively Targeting Secreted Frizzled-Related Protein-2 (SFRP2), Which is a Secreted Protein Overexpressed Across Various Cancers

- Novel therapeutic selectively antagonizing SFRP2 resulting in blockage of a pathway that impacts four key cell types associated with cancer across most solid and hematological tumors
  - IVT-8086 rescues exhausted T-cells, increases IFN- $\gamma$  and M1/M2 ratio, increases tumor apoptosis, and inhibits angiogenesis
  - No other cancer treatment impacts these 4 cell types simultaneously in cancer
- IVT-8086 has broad treatment opportunities across most solid and hematological cancers as monotherapy and in combination with PD-1 inhibitors
- Safe therapy with compelling efficacy as monotherapy and combination with other therapeutics ( i.e., checkpoint inhibitors)
- IVT-8086 administration lowers SFRP2 levels, where lower SFRP2 levels shown to correlate with better survival outcome in cancer patients
- Targeting SFRP2 with administration of IVT-8086 inhibits CD38 only in cells that express SFRP2, which is restricted to the tumor and tumor microenvironment and not normal hematopoietic cells
  - IVT-8086, by antagonizing SFRP2 and inhibiting CD38 in the tumor and the tumor microenvironment has been shown to improve efficacy of PD-1 inhibitors in combination without off target toxicity
  - This pattern of improved efficacy of IVT-8086 in combination with PD-1 inhibitors should occur across most other cancers

# \$40M Financing to Complete Plan for Development of IVT-8086 (hSFRP2 mAb), and Development of Diagnostic – 3 Year Development Timeline

\$11M Funding Raised to Date has been Non-Dilutive

