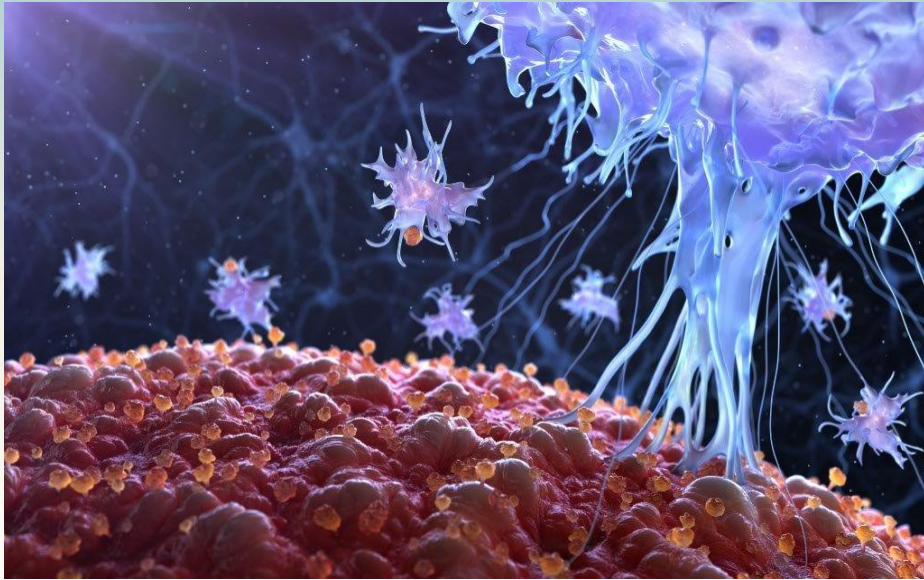


# Improving Lives of Patients with Cancer



***“This 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

Lead humanized mAb selected, IVT-8086, has been shown to antagonize SFRP2 by **selectively blocking the non-canonical Wnt/Ca2+ pathway which significantly reduces tumor growth across multiple cancers**

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

- 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**

Highly Experienced Management/Development Team with a Successful Track Record

- 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

Defined Regulatory Development Pathway and Robust IP Portfolio

- 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 \$100-300M)**
- **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



**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



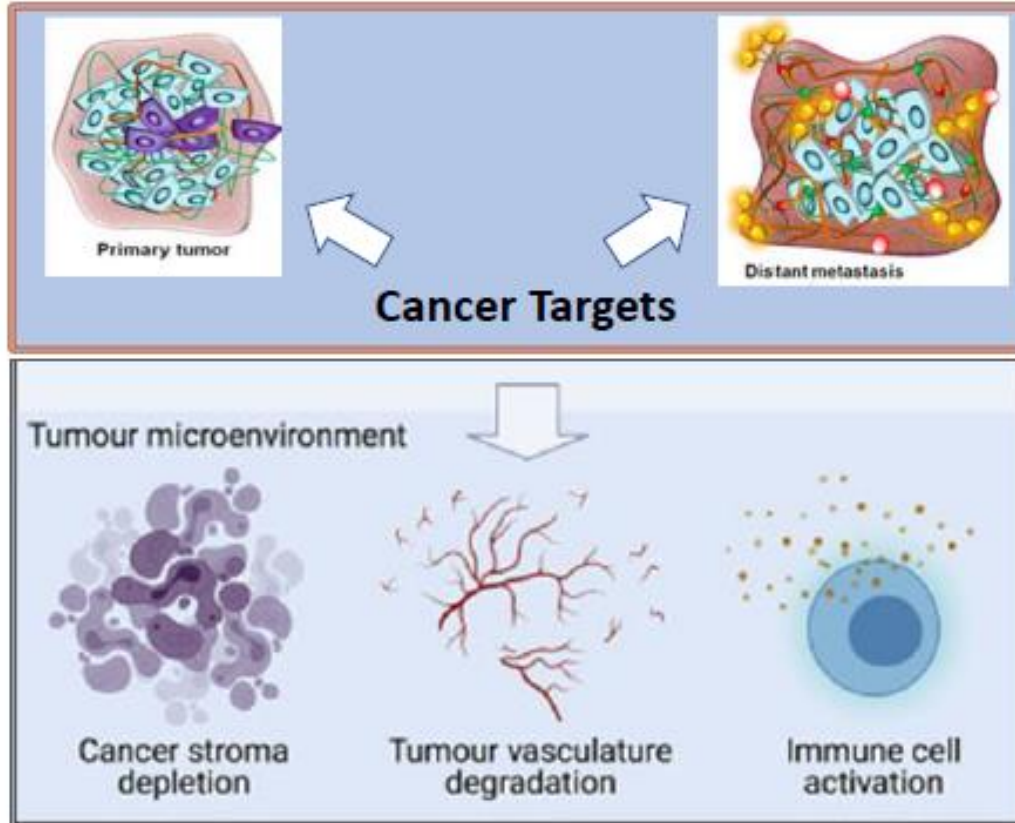
**Steve Cole**  
Head of BD and Licensing

Highly experienced Business Development/Licensing executive with 40+ years of global industry experience.



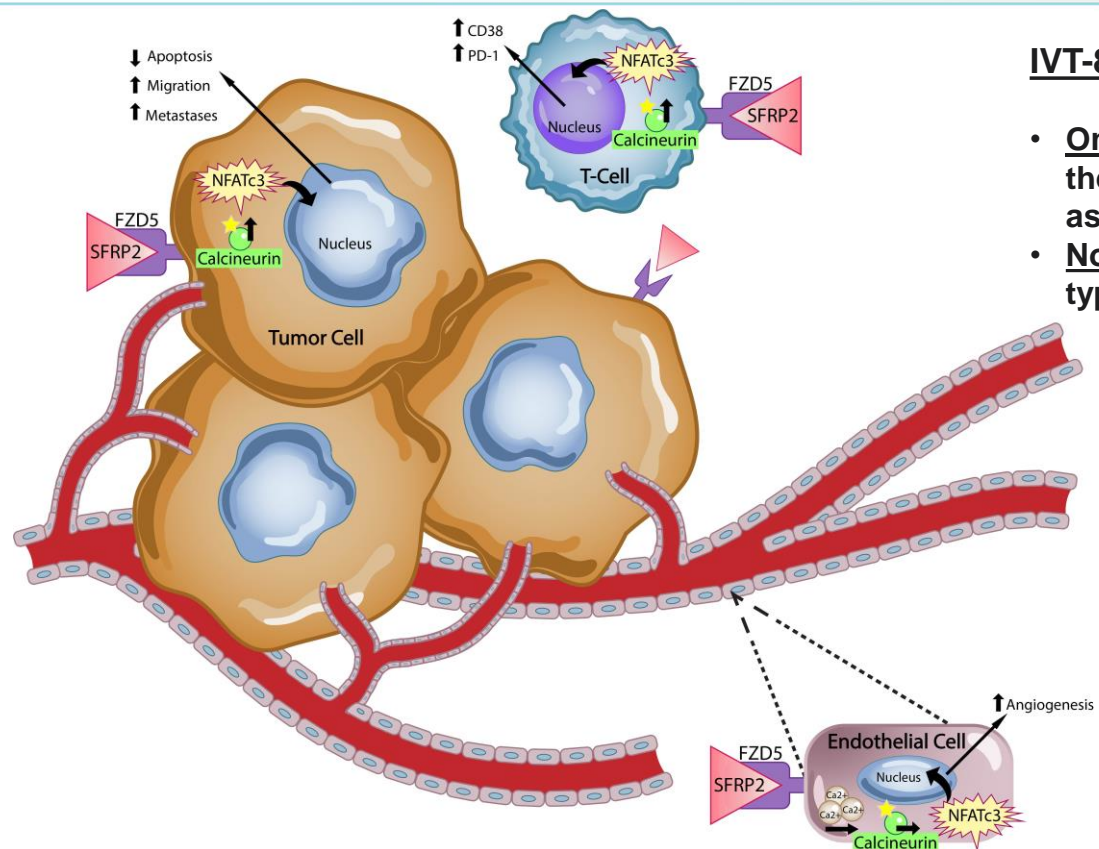
# Various Targets of Cancer Therapeutics

## 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, and T-Cells, Effecting Tumor Growth and Metastases, Angiogenesis, and T-Cell Exhaustion



### IVT-8086 (humanized monoclonal antibody)

- Only therapeutic targeting SFRP2 and blocking the pathway that impacts three key cell types associated with cancer across most tumors
- No other cancer treatment impacts these 3 cell types simultaneously when cancer is present

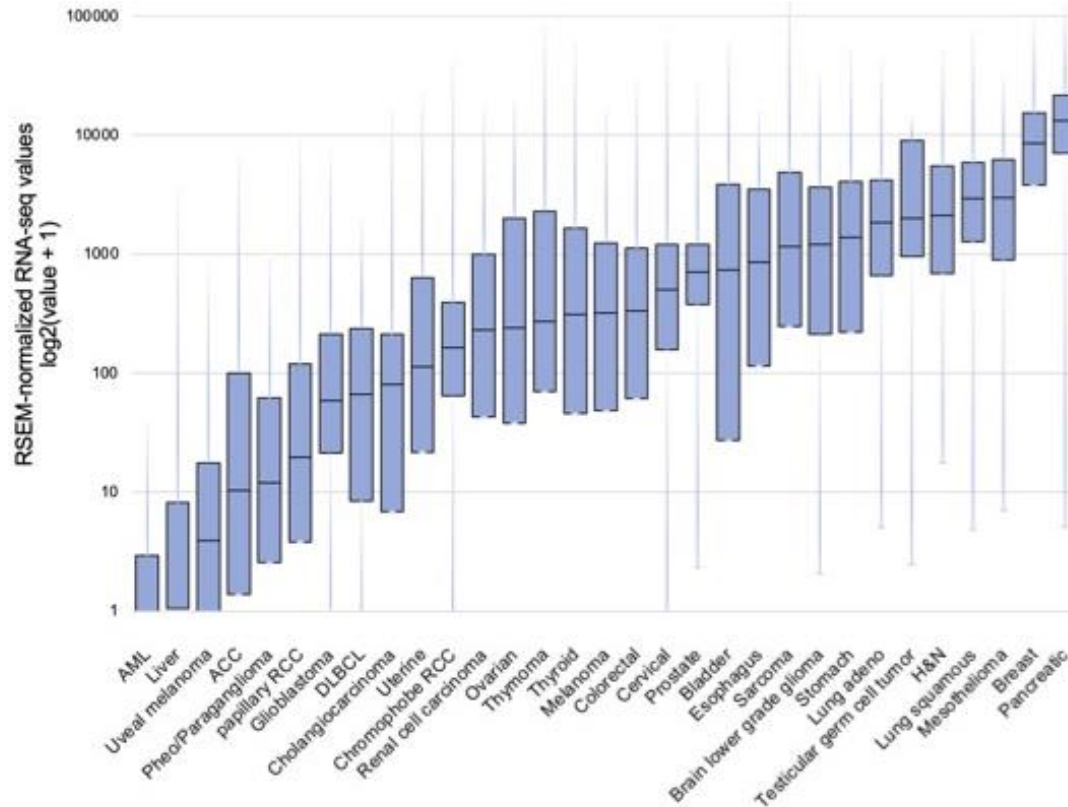
Klauber-DeMore Lab Pubs, Bhati, R. et al., Am J Pathol, 2008  
 Courtwright, A. et al, Cancer Research, 2009  
 Siamakpour-Reihani, R. et al. Plos One, 2011  
 Fontenot, E. et al., Mol Cancer Ther., 2013 Tsuruta, JK Plos One, 2014, Tsuruta, JK Plos One, 2017  
 Peterson, YK et. Al., Angiogenesis, 2017

# 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 in vivo; increases apoptosis, decreases angiogenesis, decreases NFAT activation.
Angiosarcoma and Osteosarcoma	IVT-8086 inhibits angiosarcoma and osteosarcoma in vivo; 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 in vivo
Breast	Overexpression of transfected SFRP2 in MCF7 breast cancer cells increased their resistance to apoptotic signals in vitro.  SFRP2 overexpression in vivo 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)	RPM18226 and U266 MM cell lines and primary MM cells suppress in vitro 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 in vitro, 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 in vitro and enhanced metastatic potential in vivo.
Alveolar and soft tissue sarcomas	A query of TCGA data comparing relative expression of SFRP2 (cBioPortal for Cancer Genomics) across a panel of different tumor types demonstrating high expression in sarcomas
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 is Overexpressed Across Many Tumor Types

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



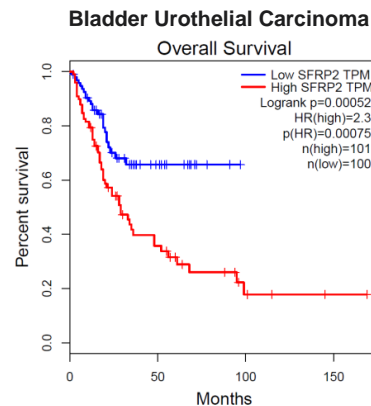
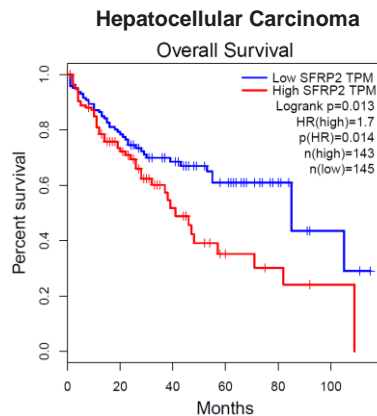
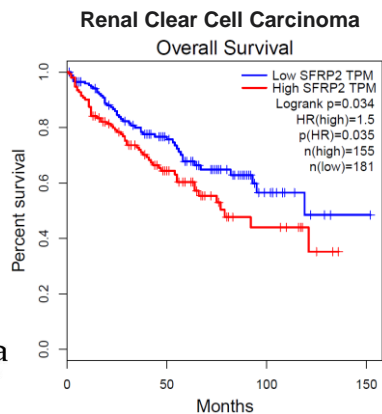
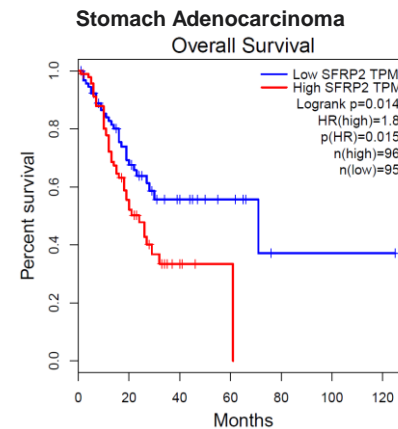
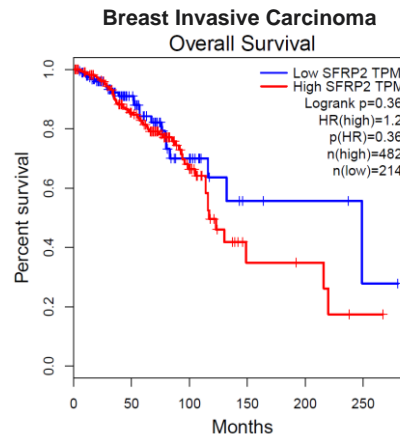
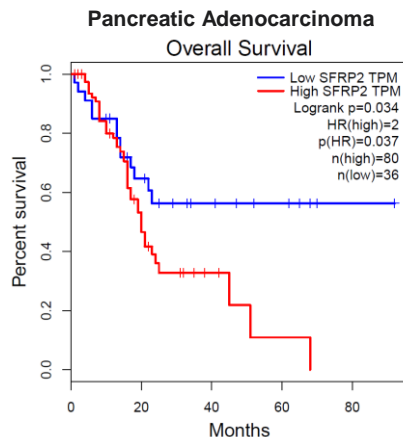
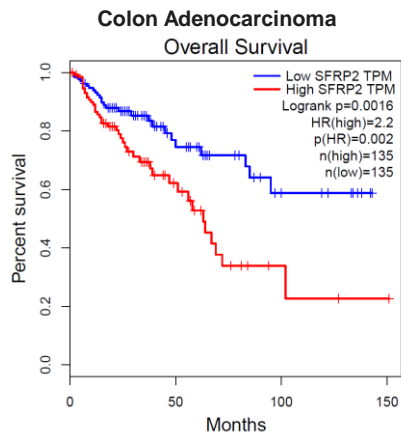
**Initial cancers targeted:**  
Pancreatic, Breast Cancer,  
and Sarcomas including  
osteosarcoma have high  
SFRP2 RNA expression

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



# SFRP2 mRNA Expression Levels Correlate with Survival in Cancer Patients

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



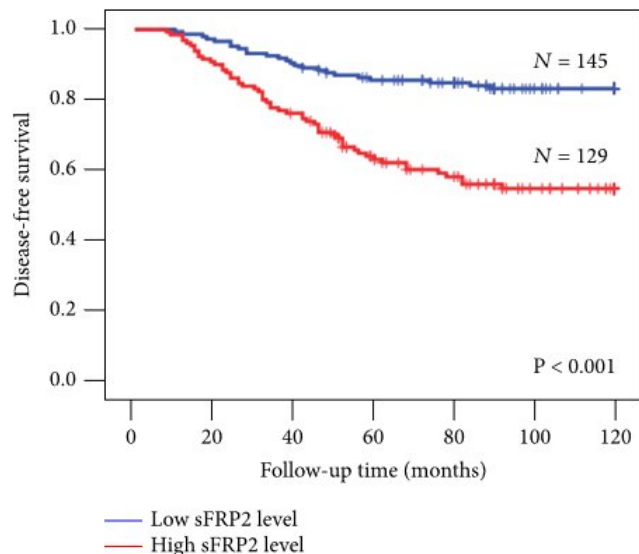
**GEPIA is a interactive web server for analyzing the RNA sequencing expression data of 9,736 tumors and 8,587 normal samples from the TCGA and the GTEx projects.**

**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 Levels in Serum Demonstrated to Correlate with Various Tumor Assessments Including Patient Outcome

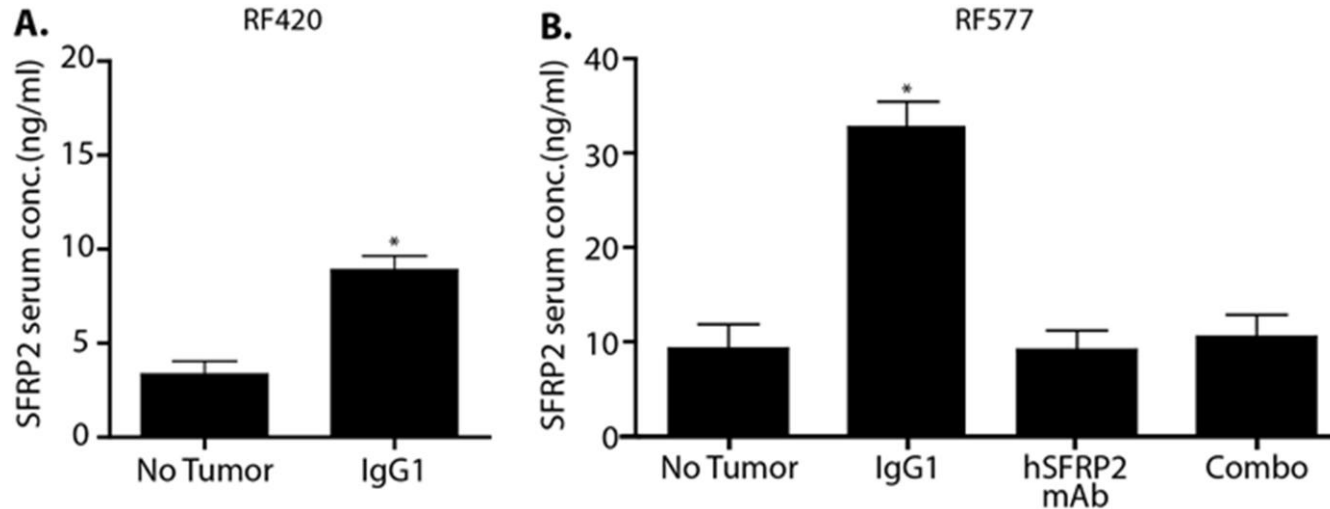
- SFRP2 serum concentrations compared between 274 breast cancer patients and 147 healthy controls
- SFRP2 elevated in breast cancer patients compared to normal
- SFRP2 levels are positively associated with tumor size, lymph node metastases, TNM stage, and Ki67 rate.
- SFRP2 serum levels associated with 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.

# Serum SFRP2 is Elevated in Mice with Osteosarcoma and Reduced After Treatment



- A) Serum levels of SFRP2 were compared between C57/BL6 mice with metastatic RF420 OS treated with IgG1 control for 21 days and C57/BL6 mice without tumors with ELISA. There were significantly higher levels of SFRP2 in the serum of mice with metastatic RF420 OS versus normal mice (n=3, \*p<0.01).
- B) ELISA was used to compare the serum levels of SFRP2 in all treatment groups of the C57/BL6 mice with metastatic RF577 OS and C57/BL6 mice without tumors. The serum level of SFRP2 was significantly higher in the IgG1 group compared to no tumor (\*p<0.01). The serum level of SFRP2 was decreased in the hSFRP2 mAb (IVT-8086) (n=12), and Combo (n=12) treatment groups compared to IgG1 treated mice.

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.

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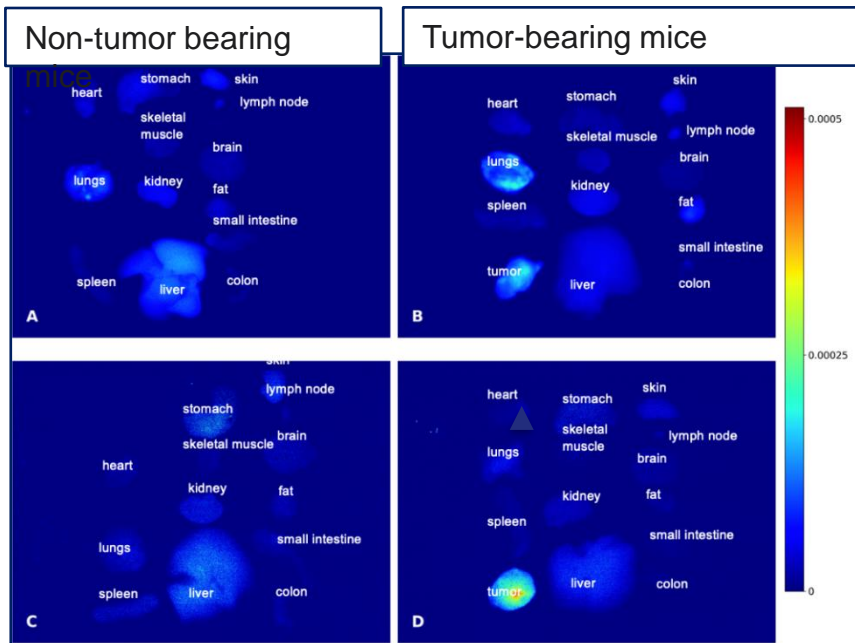
## SFRP2 Cancer Diagnostic in Development as a Sensitive Test for Early Cancer Screening, as a Prognostic Marker for Assessing Patient Benefit, and Marker of Reoccurrence

### *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



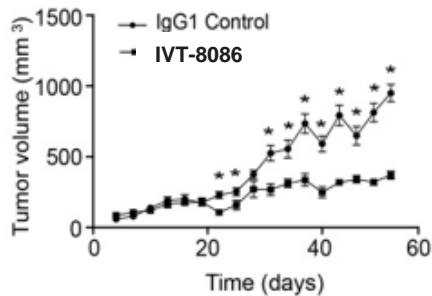
Methods: Mice were injected with 5 million MDA-MB-231 cells. Treatment of IVT 80-86 or IgG1 control iv at 4 mg/kg in 100  $\mu$ L.

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

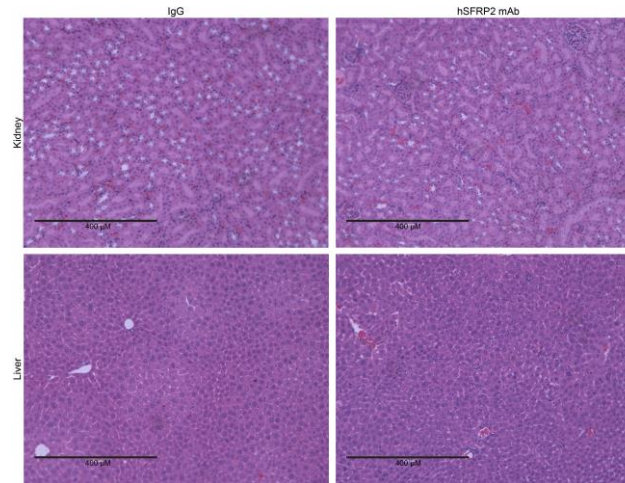
# IVT-8086 Significantly Reduced Tumor Growth in A Highly Chemoresistant Hs578T Triple Negative Breast Tumor *in vivo* with No Signs of Toxicity

## Metaplastic Triple Negative Breast (Hs578t) CHEMORESISTANT



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

- 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.



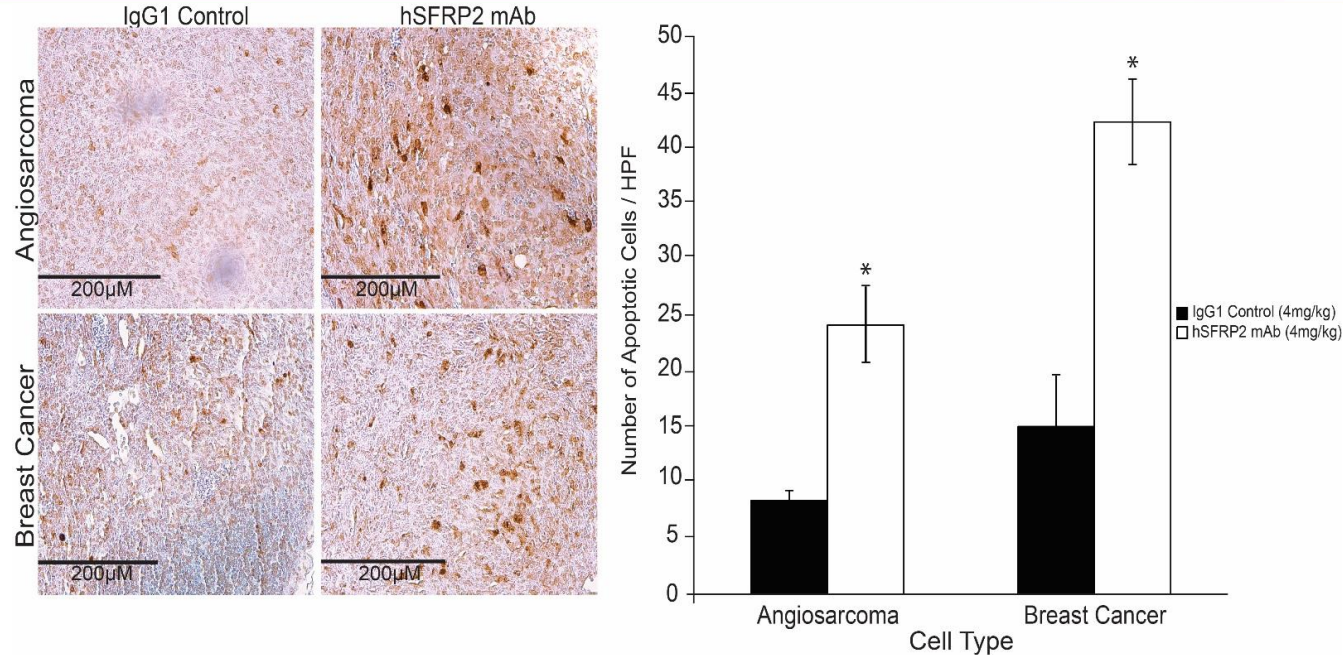
There were No Histological Changes in the Liver and Kidneys Following Multiple Dosing Administration at 4 times the Efficacious Dose (20 mg/kg) of IVT-8086 in Mice Injected with Angiosarcoma Cells

Nude mice with Hs578t 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.

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

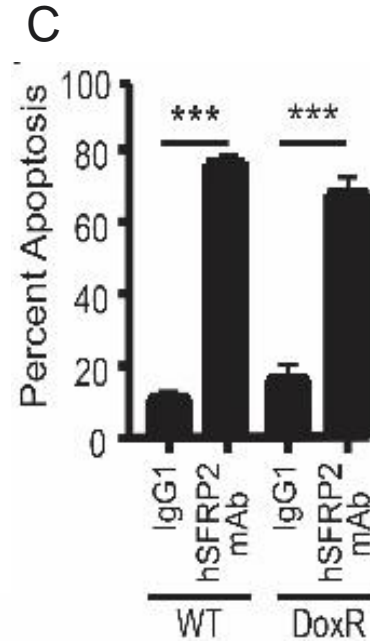
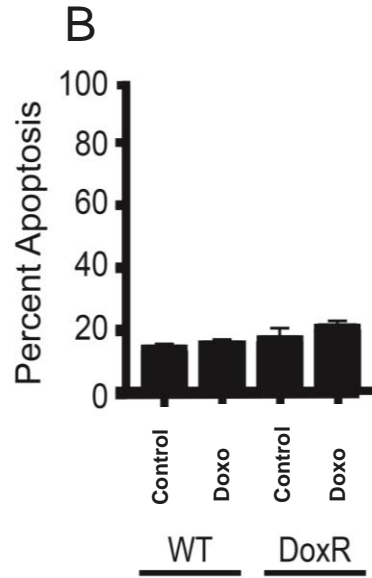
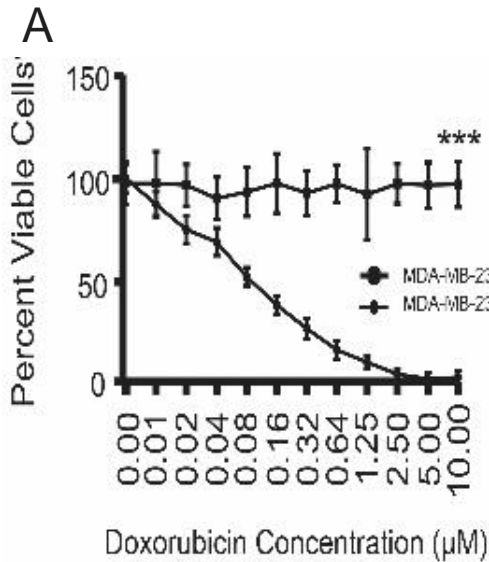


IVT-8086 promotes apoptosis in tumors. (Left) Paraffin embedded SVR angiosarcoma (upper panels) and Hs578T metaplastic breast cancer (lower panels) were sectioned and processed for TUNEL staining. The number of apoptotic cells (brown) was counted in each field. A total of 10 tumors per treatment (n=10) 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

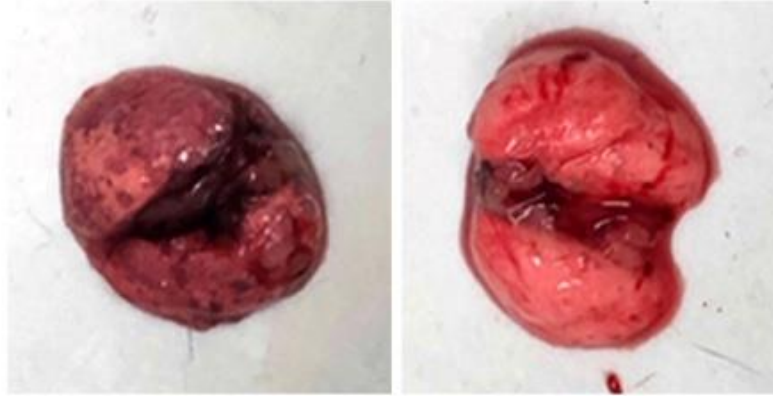
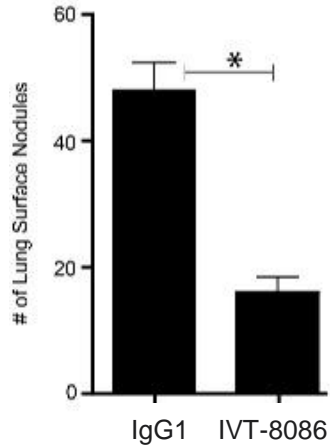
# IVT- 8086 Induces Tumor Apoptosis in TNBC Cells Resistant to Doxorubicin (DoxR)



- A. MDA-MB-2312 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

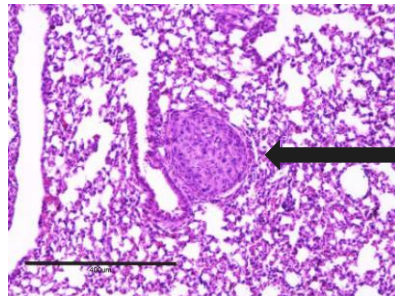


# IVT-8086 Reduces Established Metastatic Osteosarcoma in Mouse GEMM Model as Monotherapy and Reduces CD38 in T-Cells

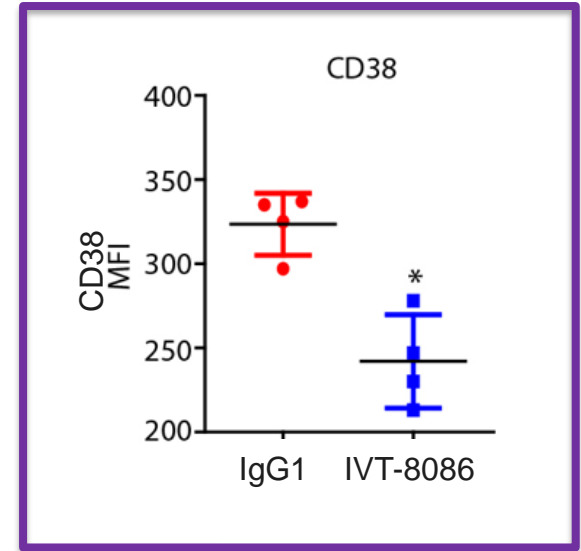


Osteosarcoma RF420 cells from a **Osteosarcoma GEMM model** were injected intravenously in C57BL6 mice. Treatments with an IgG1 control or IVT-8086 (4 mg/kg iv every 3 days), starting 10 days after the injection of tumor cells when lung mets were established. Three weeks later, the animals were euthanized,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

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



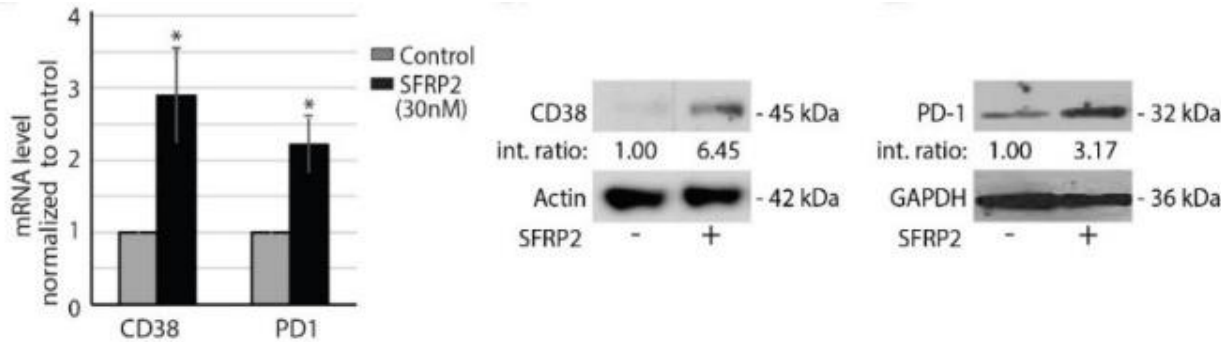
Histological confirmation of established lung mets by Day 7



\* $p \leq 0.02$

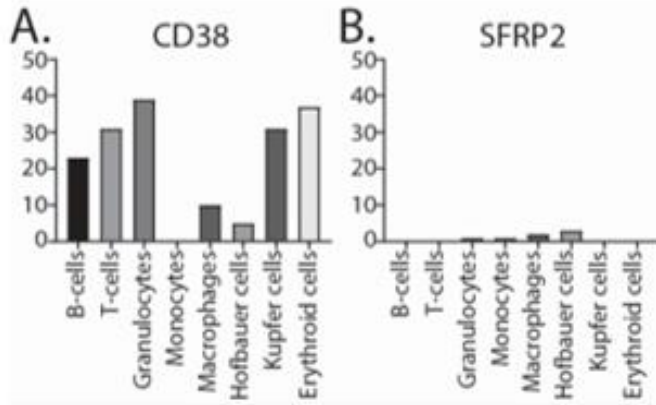
Nasarre, P. et al. Overcoming PD-1 Inhibitor Resistance with a Monoclonal Antibody to Secreted Frizzled- Related Protein 2 in Metastatic Osteosarcoma. *Cancers* 2021, 13, 2696.

# SFRP2 Increases CD38 and PD-1 mRNA and Protein in T-cells



Left: Splenic T-cells treated with or without SFRP2 (30nM) for 1h and the mRNA levels for CD38 were measured by qRT-PCR (n=8). Middle) T-cells treated with SFRP2 30 uM for 1 hour, cells were lysed, and Western blot probed for cD38 showed increased in CD38 and (right) PD-1 SFRP2-treated T-cells, compared to untreated.

# 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 only for multiple myeloma (MM) (**net sales \$6B**) which binds directly to CD38 wherever it is 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

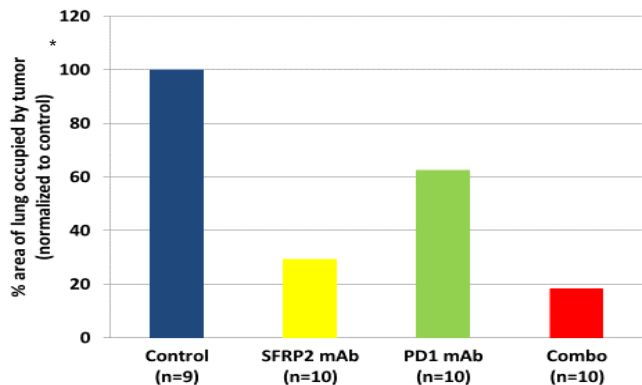
- **IVT-8086 administration associated with selective decreased CD38 expression in T-Cells**
- **Rescues T-Cell exhaustion**

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

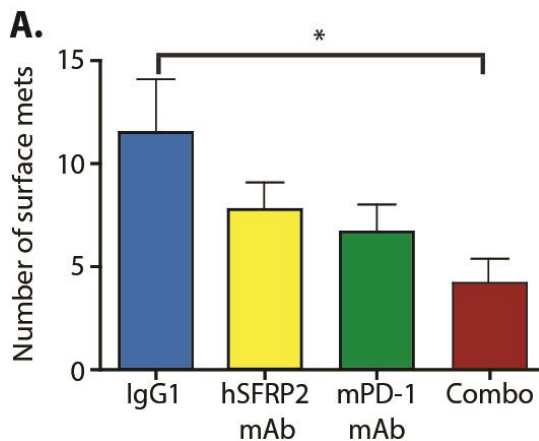
- IVT-8086, by antagonizing SFRP2, has been shown to improve efficacy of PD-1 inhibitors in combination without off target toxicity
- **This pattern of improved efficacy of IVT-8086 in combination with PD-1 inhibitors should occur across most other cancers**

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

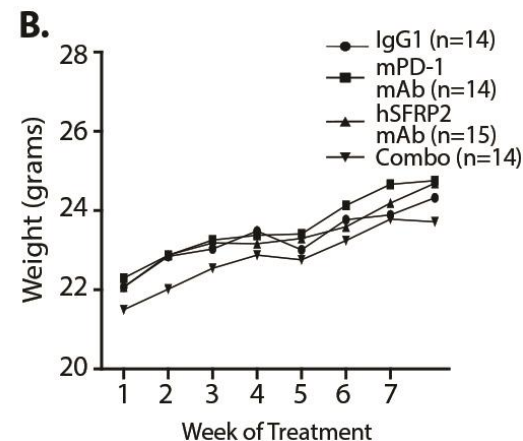
# Monotherapy and Combination Therapy Inhibits Osteosarcoma Lung Metastases in 2<sup>nd</sup> GEMM Model (RF577)



IVT-8086 treatment reduced lung metastatic tumor volume by 71%. The combination of antibodies reduced tumor volume compared to control by 82%.



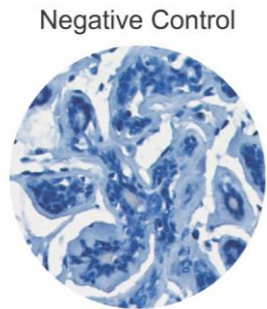
IVT-8086 treatment reduced the number of lung surface mets alone and in combination with PD-1 mAb



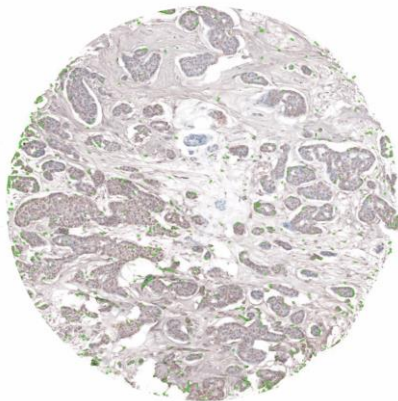
No evidence of toxicity as noted by no change in body weights in any groups during the study

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.

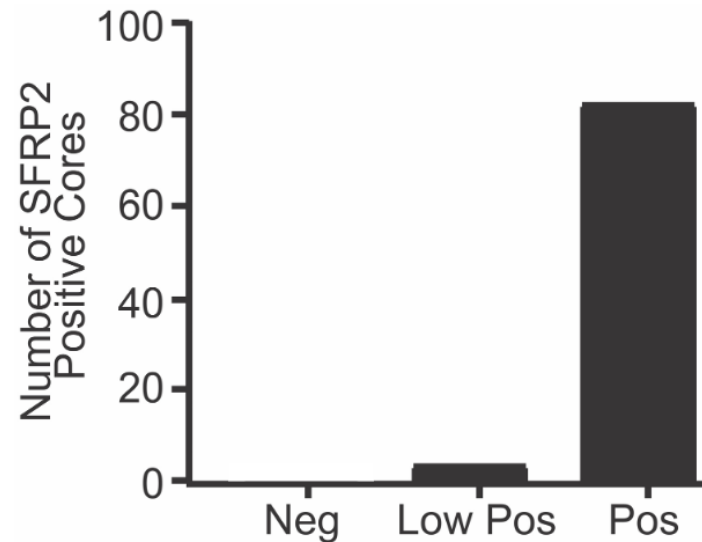
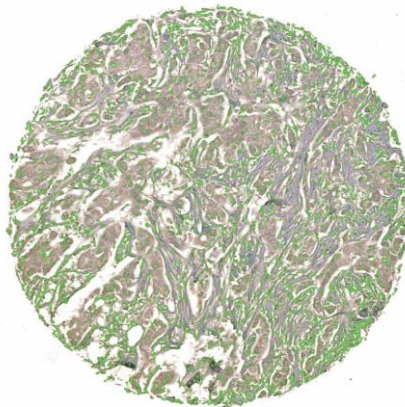
# SFRP2 is Highly Expressed in Human Triple Negative Breast Cancer (TNBC)



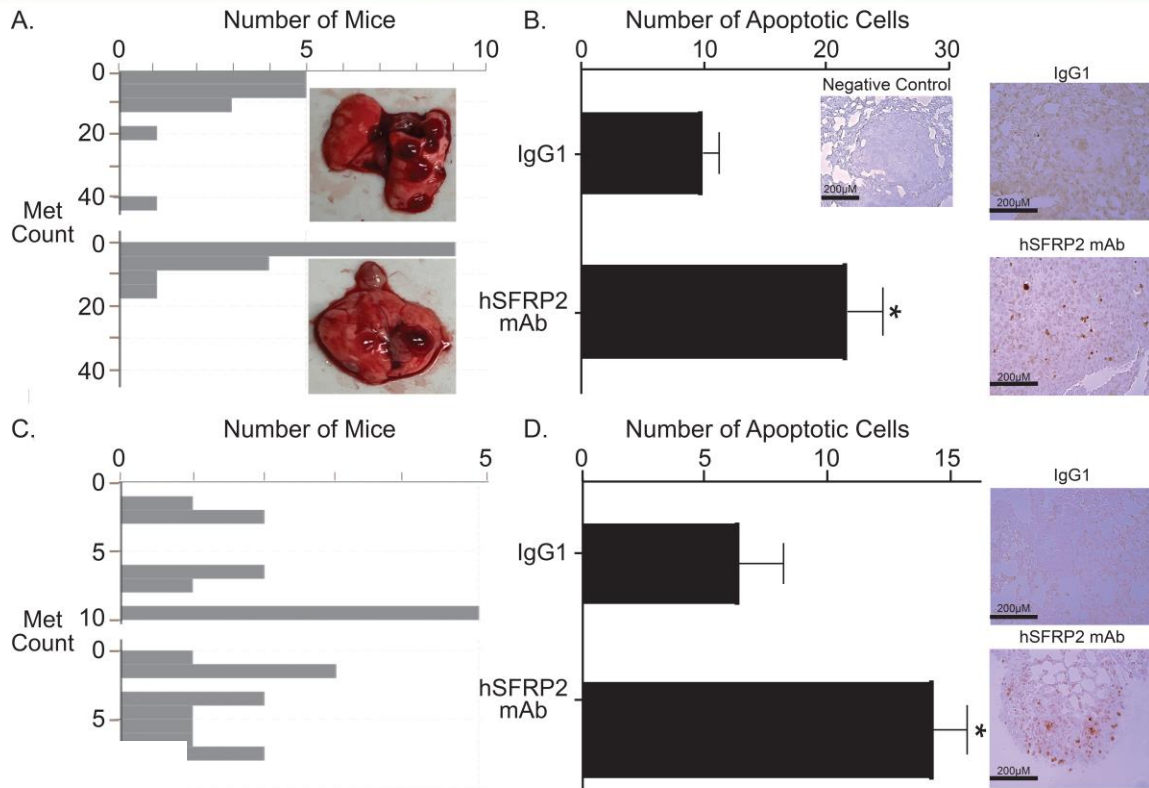
Low Positive Core



Positive Core

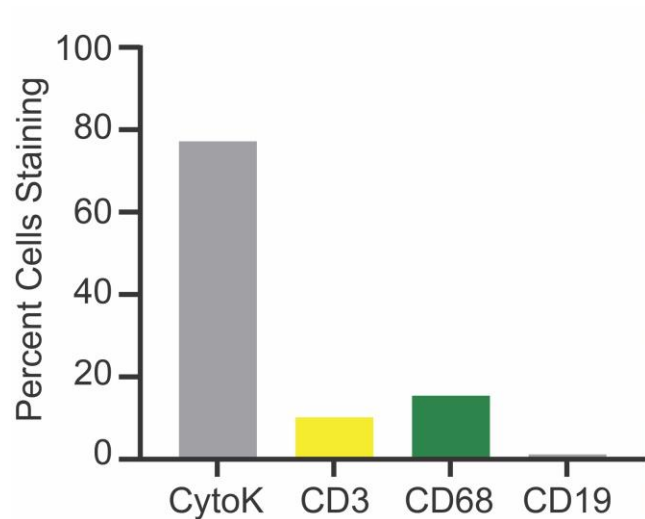


# IVT-8086 Reduces Lung Cancer Mets and Increases Tumor Apoptosis in Two TNBC Murine Models

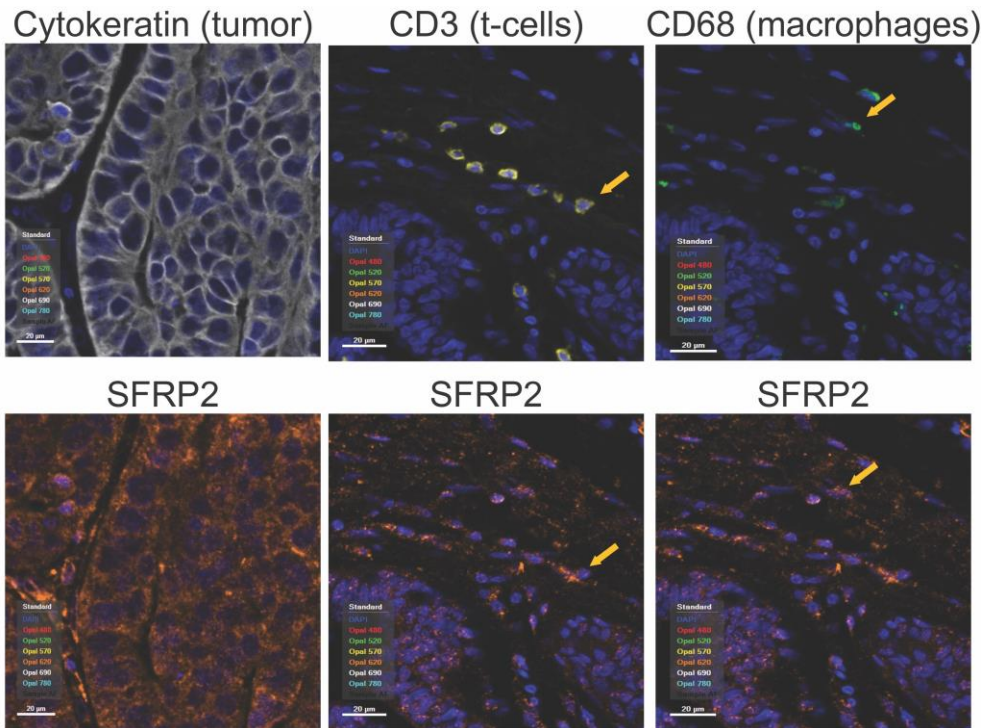


- (A) E0771.LMB TNBC cells were injected via tail vein into C57Bl6 mice and treated with IgG1 control q 7 days (representative image) or IVT-8086 mg/kg iv q 3 days (representative image). After 3 weeks, the lungs were resected, and surface metastatic lesions were counted.
- (B) TUNEL assay on FFPE E0771.LMB lung sections from mice treated with IgG1 control and IVT-8086 shows significantly more apoptotic cells in IVT-8086 treatment group (n=15, \*p,<0.05)
- (C) PY8119 TNBC cells were injected via tail vein into C57/BL6 Mice and treated with IgG1 control (n=11) versus IVT-8086 (n=11). The bar chart shows a statistically significant reduction in lung metastases in IVT-8086 treated mice compared to the control (p<0.05).
- (D) FFPE PY8119 lung slices were stained with TUNEL assay, and the number of apoptotic cells/20 x HPF were counted. **There was a significant increase in apoptotic cells in lung metastases from mice treated with IVT-8086 (n=10) compared to IgG1 control (n=10, \*p<0.05).**

# SFRP2 is Selectively Expressed in Tumor Infiltrating Lymphocytes and Tumor Associated Macrophages

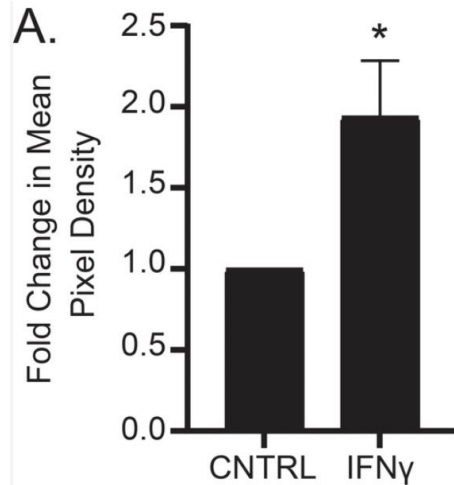


	CytoK	CD3	CD68	CD19
mean(%)	77.00	10.00	15.30	1.00
n=4 SEM	0.13	0.04	0.06	0.01

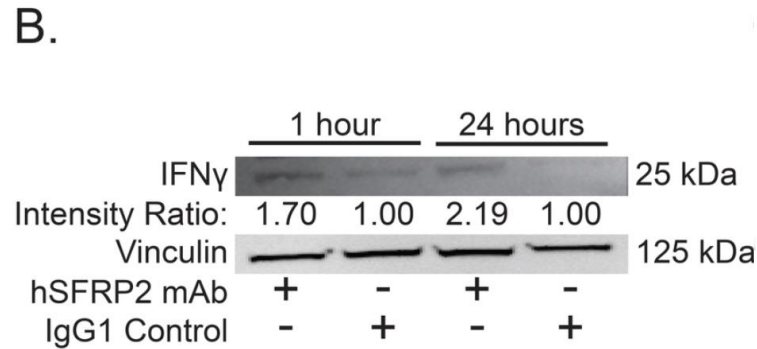


# IVT-8086 Increases IFN- $\gamma$ secretion in TAMS

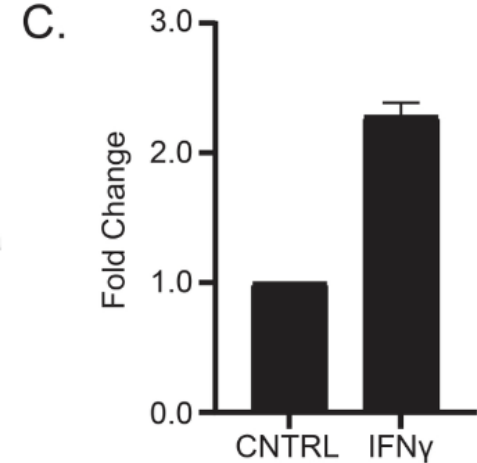
## Cytokine Array



## Western Blot

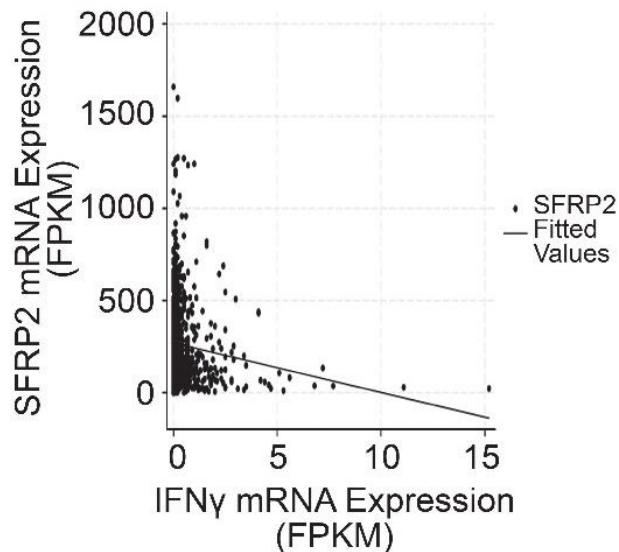


## RT PCR





# SFRP2 Inversely Correlated with INF- $\gamma$ in Human Breast Cancer



To further evaluate the relationship between SFRP2 and INF- $\gamma$ , data from The Cancer Genome Atlas (TCGA) was obtained through the Human Protein Atlas.

Our study involved 1075 breast cancer patients from the TCGA database who had available data on both SFRP2 .

The least squares linear regression results revealed a significant negative association between SFRP2 mRNA expression and INF- $\gamma$  expression ( $p < 0.0001$ ), corroborating our in vitro findings

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

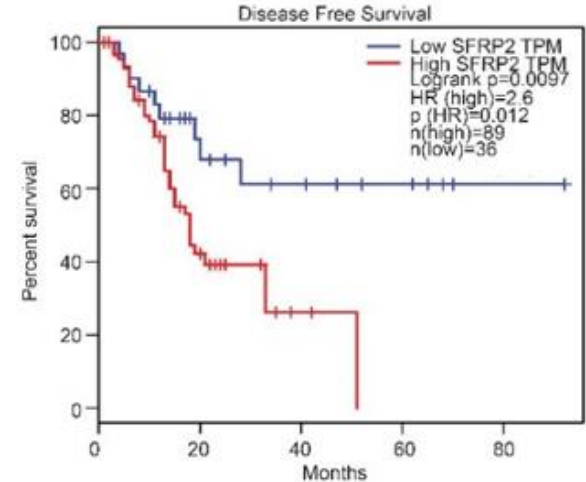
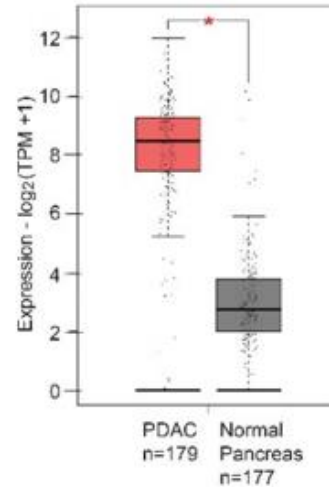
- SFRP2 is expressed in a high percentage of patients with TNBC
- SFRP2 localizes to the tumor immune microenvironment
- Antagonizing SFRP2 will inhibit the growth of metastatic TNBC
- A mechanistic rationale for IVT-8086: increasing interferon gamma (INF- $\gamma$ ) secretion in TAMs

# 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.

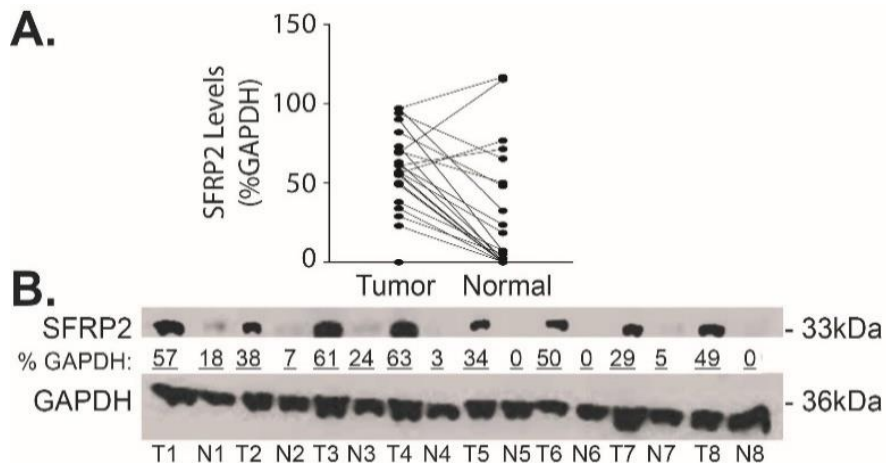
# SFRP2 is Elevated in Pancreatic Ductal Adenocarcinoma (PDAC) and Prognostic for Survival using TCGA

- 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

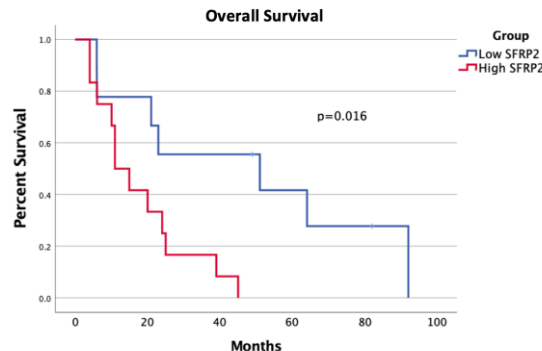
## SFRP2 is an Independent Prognostic Factor for Poor Prognosis



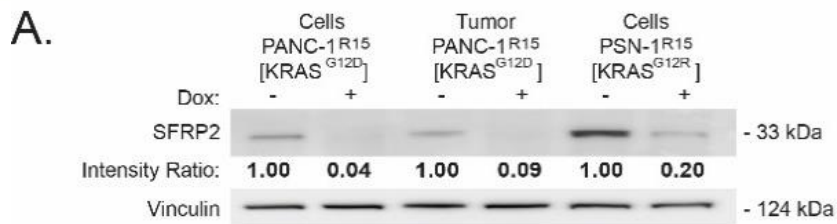
**(A)** Western blot comparing the levels of SFRP2 between tumor tissue from patients and their normal adjacent pancreatic tissue.

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

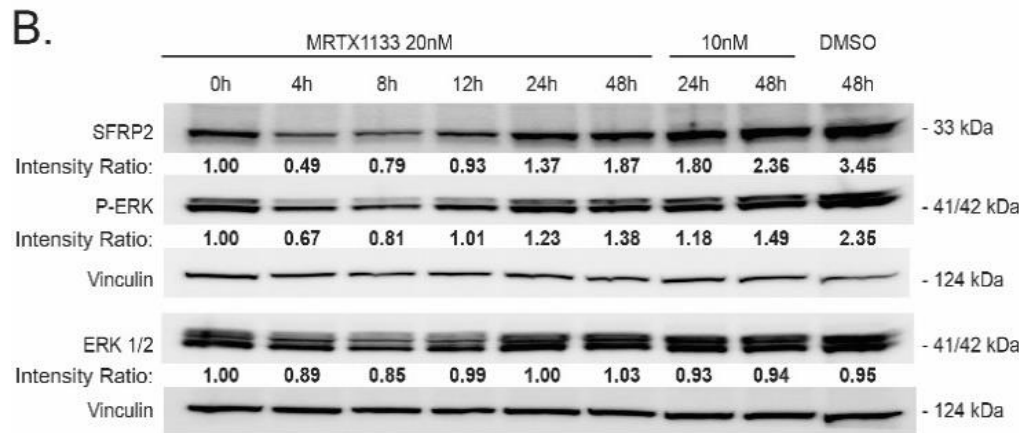
- In patients with Stage 1 and Stage 2 PDAC cancer undergoing pancreatic resection at Medical University of South Carolina (MUSC), SFRP2 protein was elevated compared to adjacent normal tissue.
- SFRP2 levels in tumors even in early stage PDAC correlated with outcome



# KRAS Demonstrated to Regulate SFRP2 in vitro and in vivo



**(A)** 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.



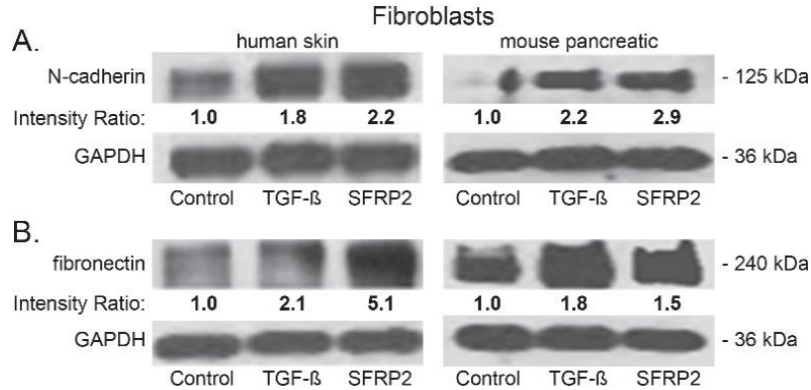
**(B)** Western blot analysis of PANC-1 cells treated with DMSO or MRTX1133 (10 or 20 nM), a noncovalent selective KRAS<sup>G12D</sup> inhibitor, for various periods of time shows a reduction of P-ERK and SFRP2 at 4 hours compared to control.

- 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

# Background on Fibrosis in Pancreatic Cancer

- Pancreatic cancer has the highest level of stroma (~80% of its mass) of any solid organ tumor which decreases the tumor vasculature and raises the interstitial pressure, shielding the tumor from chemotherapy and immune response
- Pancreatic stellate cells are considered the main driver of the desmoplastic reaction, promoting cancer progression
- The dense stroma of pancreatic cancer is a key contributor to chemotherapy resistance
- Targeting the stromal tissue for pancreatic cancer treatment may dismantle the barricade to chemotherapy and immune response

# SFRP2 Induces Epithelial Mesenchymal Transformation in Fibroblasts

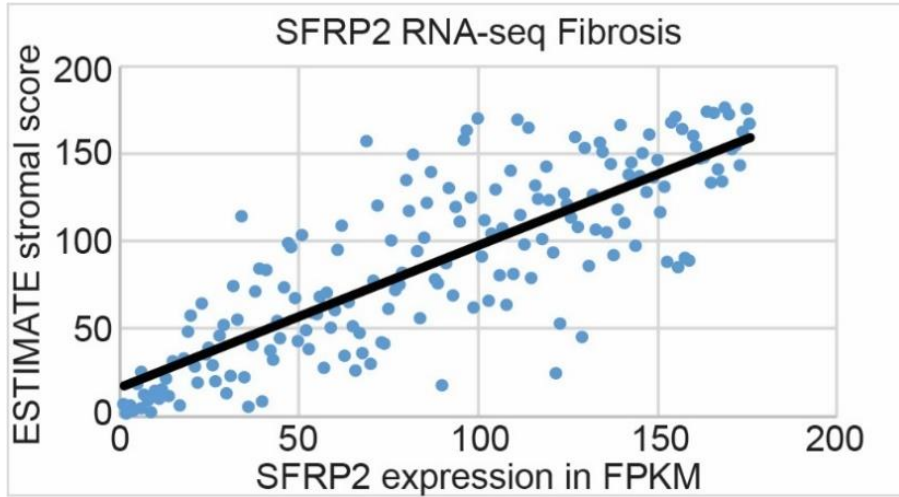


**(A)** Human skin and mouse pancreatic fibroblasts were either untreated (control) or treated for 48 hours with SFRP2 (30 nM) or TGFβ (5 nM), and protein levels were analyzed by western blot. TGFβ and SFRP2 treatments induce an increase of N-cadherin **(A)** and fibronectin **(B)** protein levels in both human skin and mouse pancreatic fibroblasts.

- SFRP2 increases N-cadherin and fibronectin in fibroblasts, greater than TGFβ (the most critical driver of fibrosis)
- Both N-cadherin and fibronectin are well-known mesenchymal markers involved in migration and invasion during tumor progression



# SFRP2 Level Associated with PDAC Fibrosis



mRNA expression of SFRP2 in PDAC patient samples from the TCGA (n=176) correlates with the ESTIMATE stromal score obtained from RNAseq data on those patients. Spearman correlation coefficient is 0.81.

Using The Cancer Genome Atlas (TCGA) Database, SFRP2 expression was positively correlated with fibrosis in PDAC

# Inhibiting Fibrosis in PDAC

- A small molecule inhibitor of the sonic hedgehog pathway showed efficacy in preclinical studies, but failed to demonstrate improved survival in clinical trials
- Some improvements have been observed with other stromal inhibitors in phase I/II trials targeting TGF $\beta$  and angiotensin II receptor
- Depleting myofibroblasts in a pancreatic cancer genetically engineered mouse models (GEMM) resulted in increased infiltration of regulatory T-cells and worse survival
  - Blocking SFRP2 with IVT-8086 resulting in simultaneous targeting of T-cells and fibrosis and may be a way to impact the efficacy in PDAC
- **IVT-8086 rescues exhausted T-cells, inhibits tumor apoptosis, inhibits angiogenesis, and inhibits fibrosis. These combined effects suggest that IVT-8086 could be a very effective therapeutic as monotherapy for PDAC**

# Clinical Development Plan Rationale for IVT-8086 Initially Focused on Four Cancers, Sarcoma (including Osteosarcoma), Breast Cancer (Including TNB), 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



- SFRP2 highly expressed in all human breast cancer subtypes, including TNBC
- In vivo inhibition in tumor growth in chemoresistant 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

## Pancreatic Cancer



- SFRP2 highly expressed in pancreatic cancer, protein levels correlation with patient survival
- 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.

## 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.

# Key Benefits of Innova Therapeutics Novel Cancer Therapeutic Platform

- **Novel** therapeutic selectively antagonizing SFRP2 resulting in blockage of a pathway that impacts three key cell types associated with cancer across most solid and hematological tumors
  - IVT-8086 rescues exhausted T-cells, inhibits tumor apoptosis, inhibits angiogenesis
  - No other cancer treatment impacts these 3 cell types simultaneously in cancer
- 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
- **KRAS regulates SFRP2 in PDAC, where SFRP2 expression is significantly associated with worse disease-free survival**
  - The oncogenic effects of KRAS should be inhibited by IVT-8086 treatment
  - SFRP2 expression is associated with fibrosis in pancreatic cancer.
  - SFRP2 induces N-cadherin and fibronectin from fibroblasts, which are associated with cancer metastases
- **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 \$100-300M)**
- **Measurement of SFRP2 in patient blood** has the potential as a **diagnostic for early cancer detection across many cancers including PDAC** and as a **prognostic marker for assessing cancer reoccurrence**
- **Global patent protection through 2042 and beyond**

# Seeking \$15M Financing Initially (Additional \$25M Raise 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

