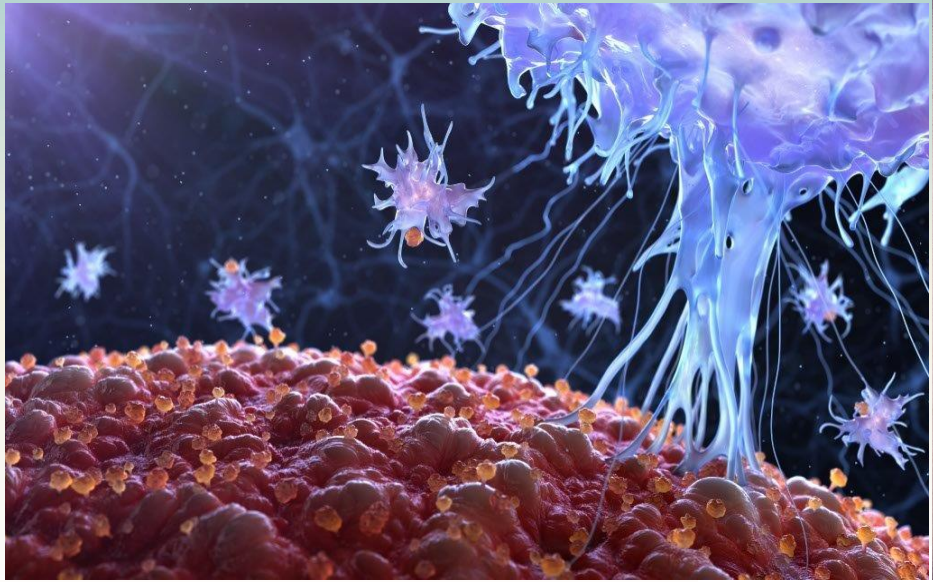
Improving Lives of Patients with Cancer



Innova therapeutics

"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 2040, 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.**
  - **4th 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

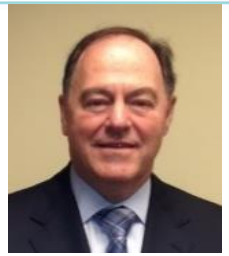
Defined Regulatory Development Pathway and Robust IP Portfolio

- 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**

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
CSO

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

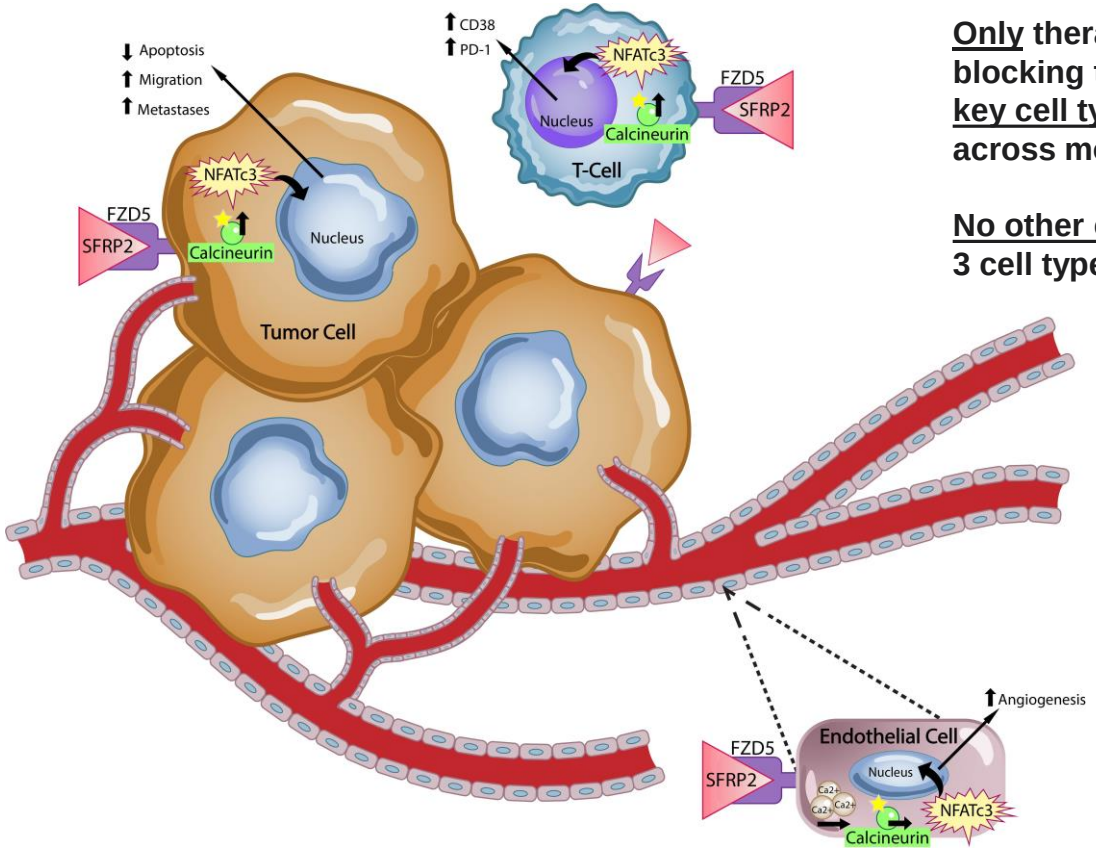
Highly experienced Clinical Operations Executive with 29+ years in the field of clinical research, including senior roles at major CRO and pharmaceutical companies

Steve Cole
Head of BD and Licensing

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

Multi-faceted Mechanism of Action

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



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 in cancer

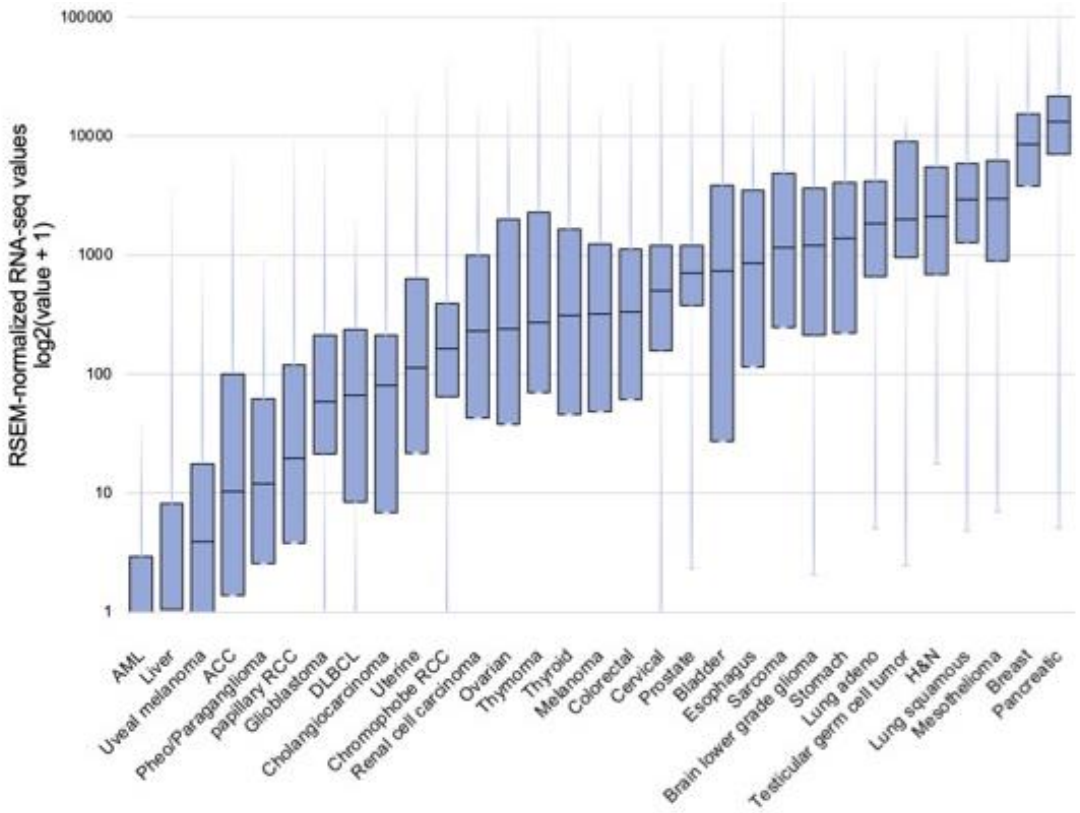
Klauber-DeMore Lab Pubs, Bhati, R. et. al., Am J Pathol, 2008
Courtwright, A. et al, Cancer Research , 2009
Siamakpour-Reihani, R. et al. Plos One, 2011
Fontenot, E. et. al., Mol Cancer Ther., 2013 Tsuruta, JK Plos One, 2014, Tsuruta, JK Plos One, 2017
Peterson, YK et. Al., Angiogenesis, 2017

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)	RPMI8226 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



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

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

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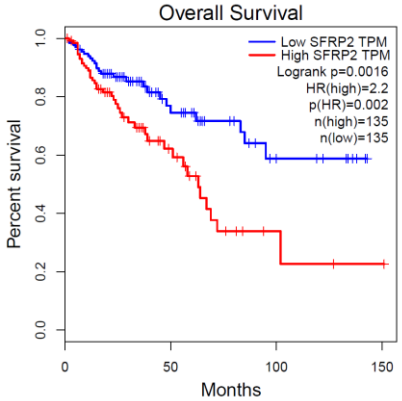
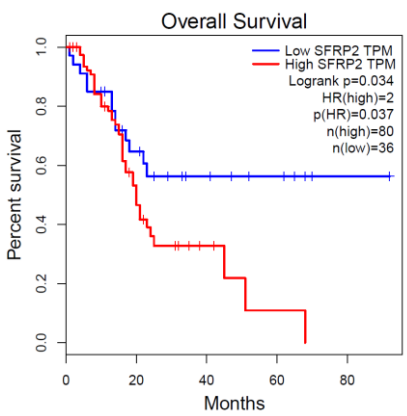
SFRP2 mRNA Expression Levels Correlate with Survival in Cancer Patients

Patients with lower SFRP2 levels in tumors have better survival outcome

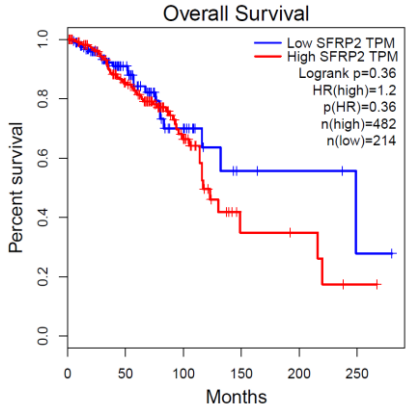
Colon Adenocarcinoma



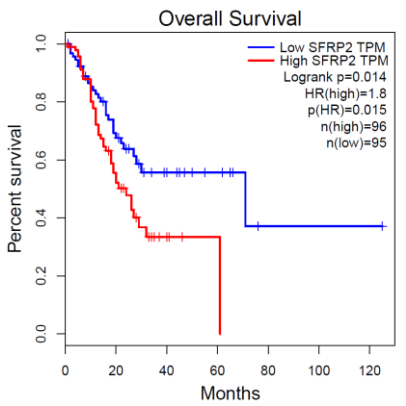
Pancreatic Adenocarcinoma



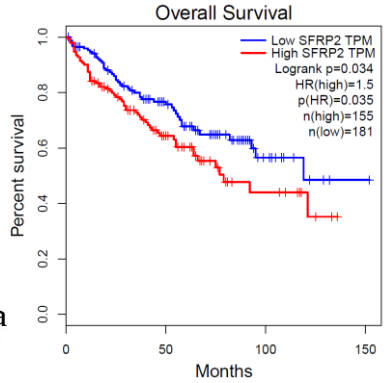
Breast Invasive Carcinoma



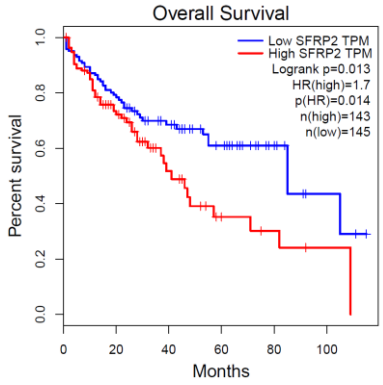
Stomach Adenocarcinoma



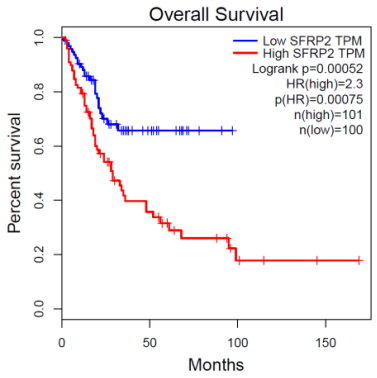
Renal Clear Cell Carcinoma



Hepatocellular Carcinoma



Bladder Urothelial Carcinoma

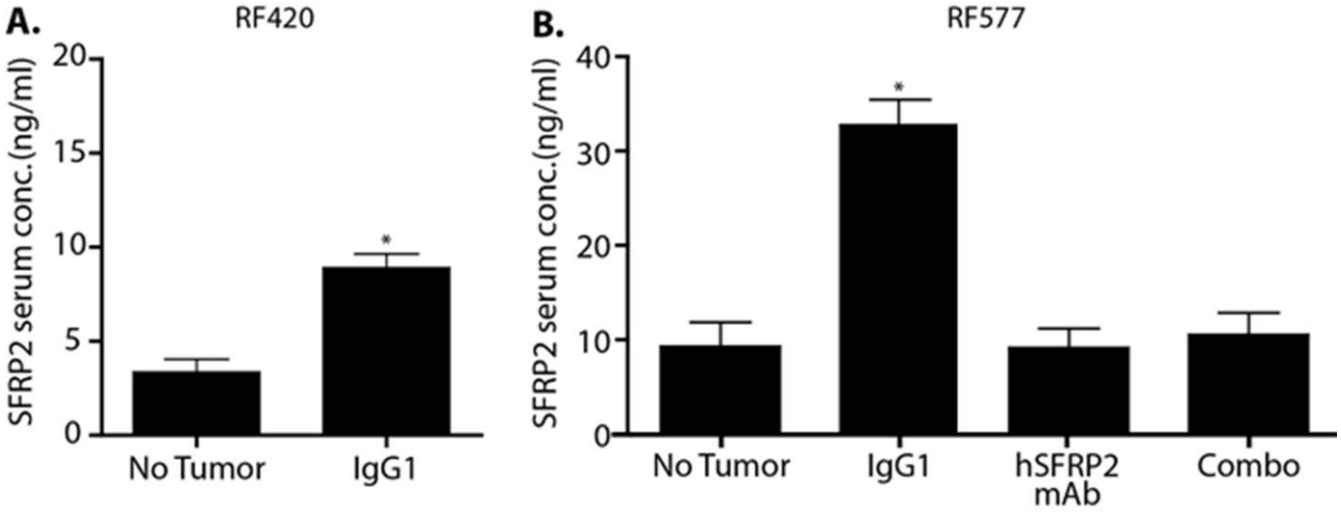


GEPIA is a interactive web server for analyzing the RNA sequencing expression data of 9,736 tumors and 8,587 normal samples from the TCGA and the GTEx projects.

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.

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 metatastic RF420 OS versus normal mice (n=3, *p<0.01).

B) 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.

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

cancers

MDPI

Article

Overcoming PD-1 Inhibitor Resistance with a Monoclonal Antibody to Secreted Frizzled-Related Protein 2 in Metastatic Osteosarcoma

Patrick Nasarre [1,†], Denise I. Garcia [1,†], Julie B. Siegel [1], Ingrid V. Bonilla [1], Rupak Mukherjee [1], Eleanor Hilliard [1], Paramita Chakraborty [1], Cécile Nasarre [2], Jason T. Yustein [3], Margaret Lang [1], Aneese A. Jaffa [1], Shikhar Mehrotra [1] and Nancy Klauber-DeMore [1,*]

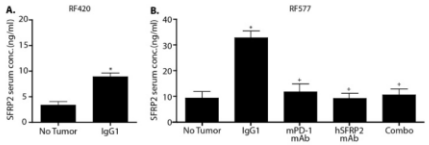


Figure 3. Serum SFRP2 levels are elevated in mice with metastatic osteosarcoma compared to non-tumor-bearing mice and responds to therapy. (**A**) Serum levels of SFRP2 were compared between C57BL/6 mice with metastatic RF420 OS treated with IgG1 control and non-tumor-bearing C57BL/6 mice with ELISA. There were significantly higher levels of SFRP2 in the serum of mice with metastatic RF420 OS versus mice without tumors ($n = 3$, * $p < 0.01$). (**B**) ELISA was used to compare the serum levels of SFRP2 in all treatment groups of the C57BL/6 mice with metastatic RF577 OS and C57BL/6 mice without tumors. The serum level of SFRP2 was significantly higher in the group of tumor-bearing mice treated with IgG1 compared to non-tumor-bearing mice (* $p < 0.01$) ($n = 9$ and $n = 8$, respectively). The serum level of SFRP2 was significantly decreased in the mPD-1 mAb ($n = 8$), hSFRP2 mAb ($n = 12$) and Combo ($n = 12$) treatment groups compared to IgG1-treated mice (* $p < 0.01$).

Fig 3 shows ELISA showing SFRP2 elevated in serum of mice with osteosarcoma compared to control mice, and levels lower with monoclonal antibody treatment

- Lower SFRP2 levels directly associated with better outcome including survival

Article

Comprehensive Analysis of *SFRP* Family Members Prognostic Value and Immune Infiltration in Gastric Cancer

Dehua Liu [1], Chenyu Sun [2], Nahyun Kim [2], Chandur Bhan [2], John Pocholo Whitaker Tuason [2], Yue Chen [3], Shaodi Ma [4], Yuting Huang [5], Ce Cheng [6,7], Qin Zhou [8] and Kaiguang Zhang [1,*]

Charles Jacob *et al. J Exp Clin Cancer Res* (2022) 41:258
https://doi.org/10.1186/s13046-022-02425-y

Journal of Experimental & Clinical Cancer Research

RESEARCH Open Access

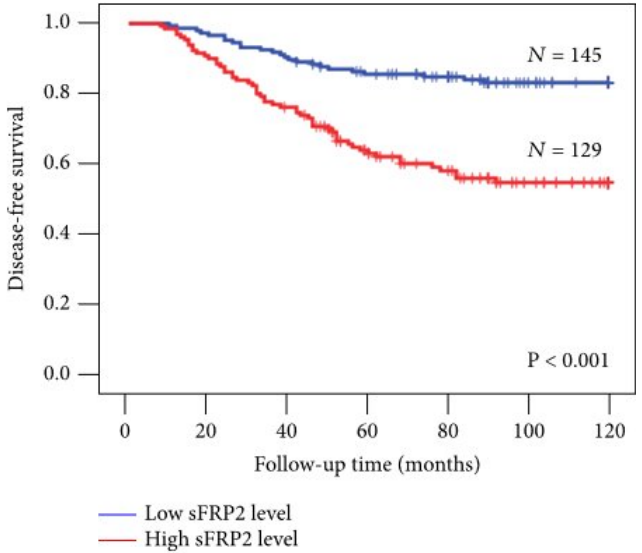
Identification of novel early pancreatic cancer biomarkers KIF5B and SFRP2 from "first contact" interactions in the tumor microenvironment

Annals of Surgery

Secreted frizzled related-protein 2 is prognostic for human pancreatic cancer patient survival and associated with fibrosis

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 (≤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.

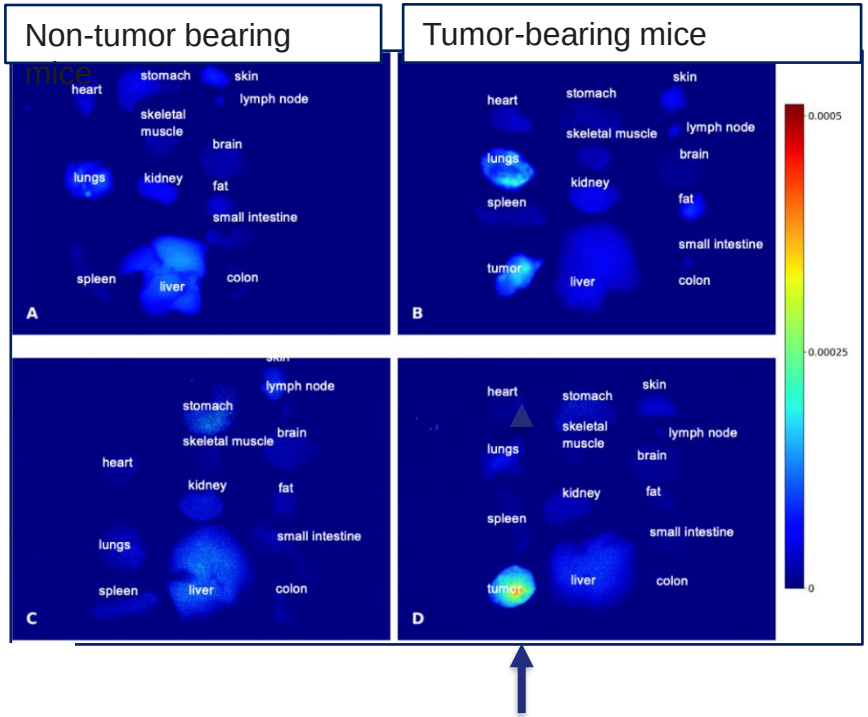
SFRP2 Shown to be a Cancer Biomarker Across Multiple Cancers

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

hSFRP2 mAb



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 µL.

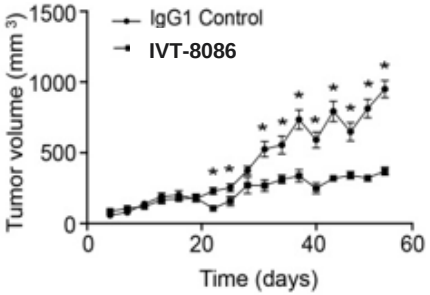
The *in vivo* kinetics of IVT 8086 was measured using treatments with NIR-conjugated antibody. Organ distribution of the mAb monitored by measuring the emission of Dylight 755 over 72 hours with the *in vivo* Maestro imaging system. After the complete metabolism of the treatment, we administered another 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

Innova therapeutics

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

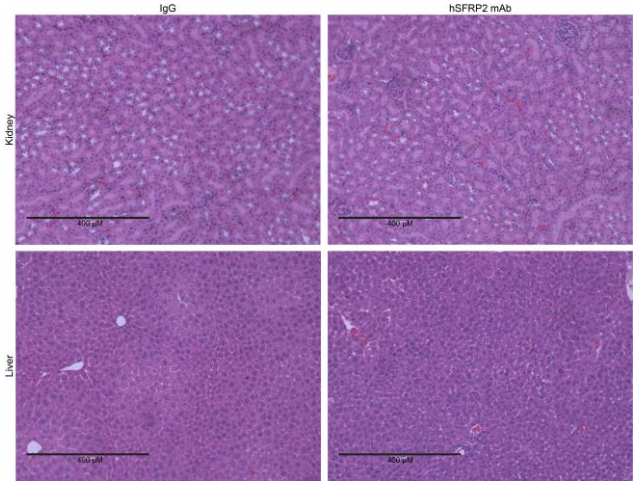
Metaplastic Triple Negative Breast (Hs578t)
CHEMORESISTANT



*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.**

Nude mice with Hs587t breast cancer xenografts **that were established (appr 100 mm³)** were treated with hSFRP2 mAb or IgG1 control every three days beginning of Day 30.

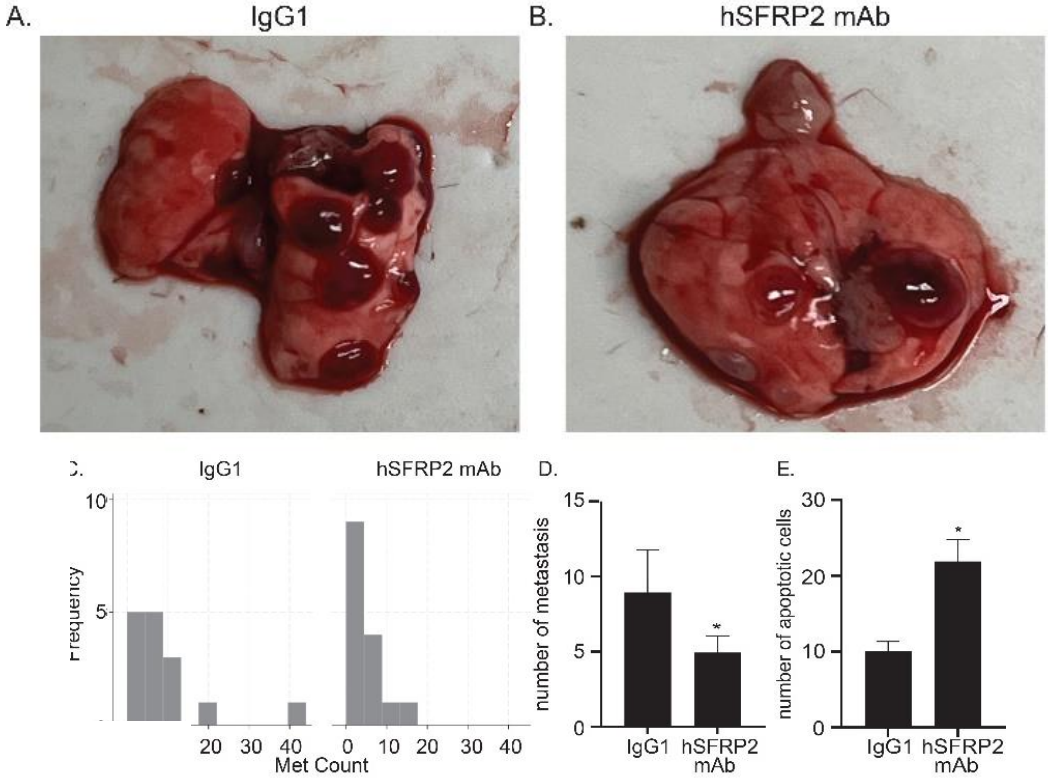


There were No Histological Changes in the Liver and Kidneys Following Multiple Dosing Administration at 4 times the Efficacious Dose (20 mg/kg) of IVT-8086 in Mice Injected with Angiosarcoma Cells

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.

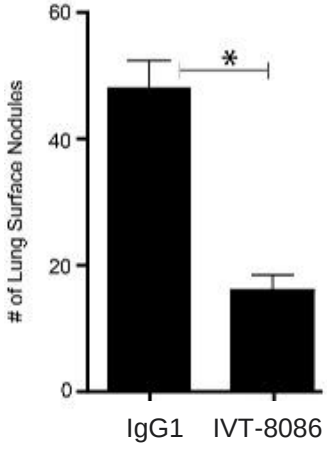
IVT-8086 Inhibits Metastatic TNBC and Increases Tumor Apoptosis

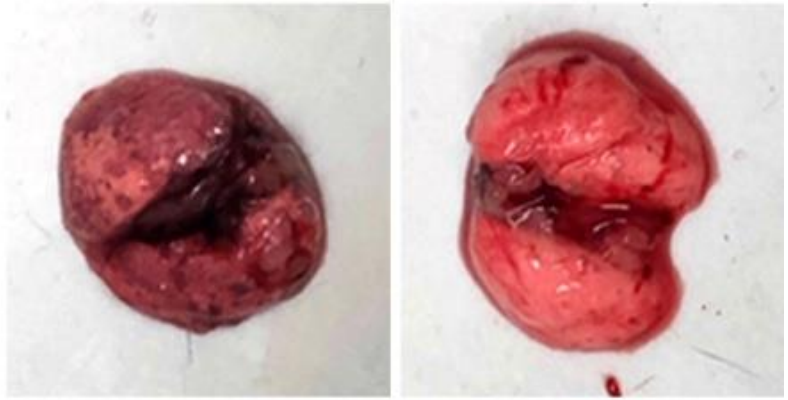


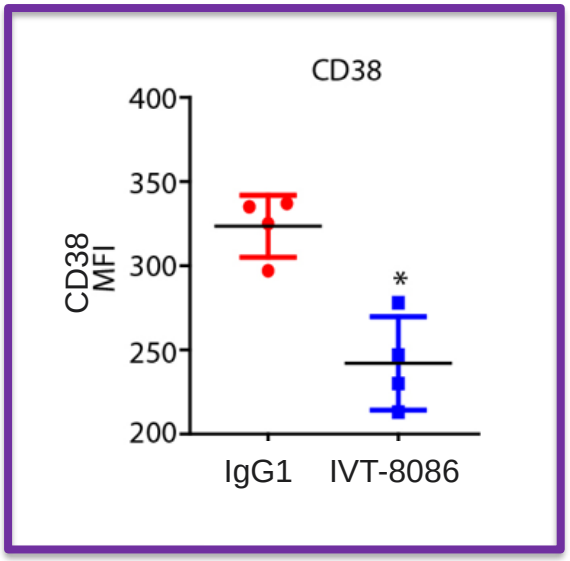
C57BL6 mice injected via tail vein with E1077 murine TNBC. Treated with control or IVT 8086. After 3 weeks lungs resected and mets in the lung counted (A-D), showing a reduction in lung mets.

E). Tunnel assay on lung mets show an increase in apoptosis in tumors treated with IVT 8086

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



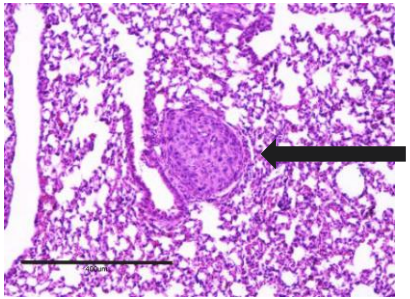




*p≤0.02

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

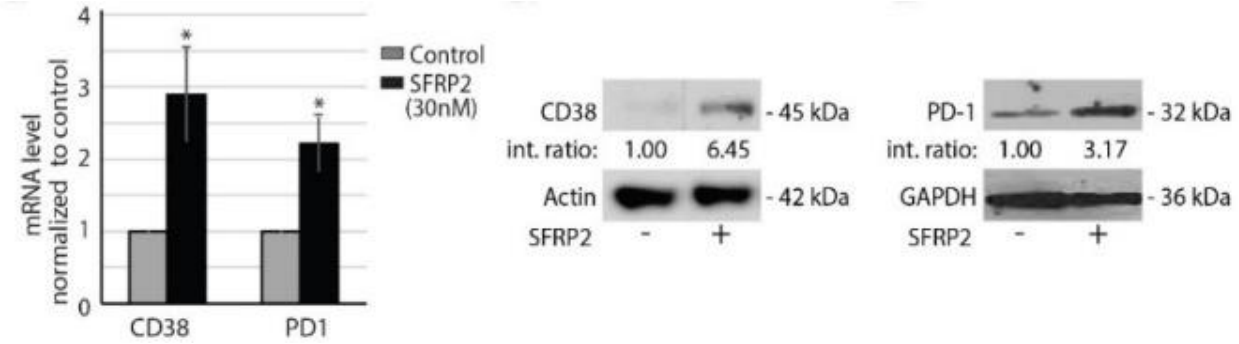
*p≤0.0001; n=12. Representative lungs with tumor



Histological confirmation of established lung mets by Day 7

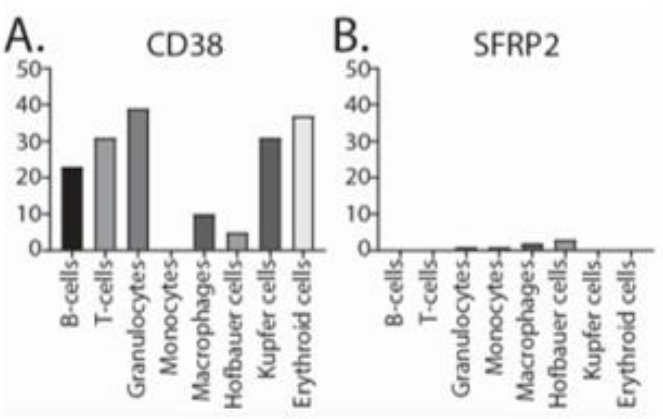
Nasarre, P. et al. Overcoming PD-1 Inhibitor Resistance with a Monoclonal Antibody to Secreted Frizzled- Related Protein 2 in Metastatic Osteosarcoma. Cancers 2021, 13, 2696.

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[1]



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 its 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

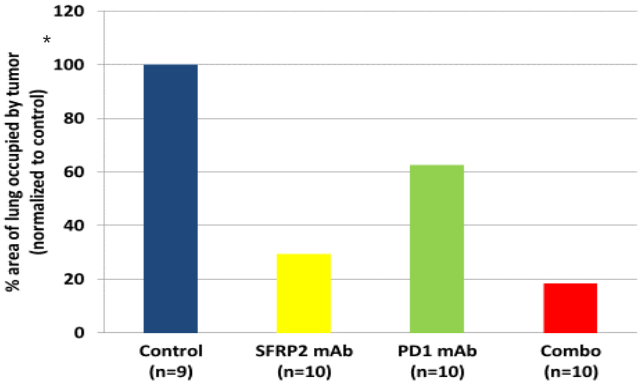
- **IVT-8086 administration associated with selective decreased CD38 expression in T-Cells**

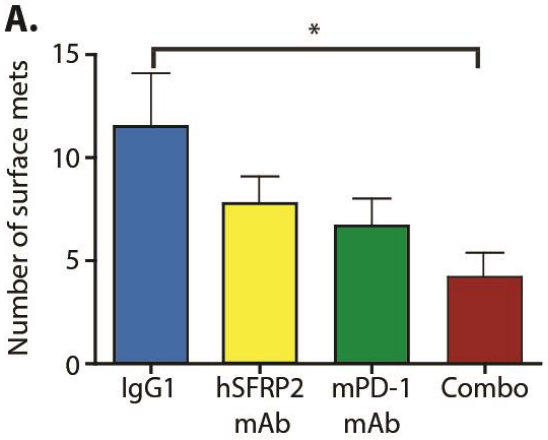
Targeting SFRP2 will specifically inhibit CD38 only in cells that express SFRP2, which is restricted to the tumor and tumor microenvironment

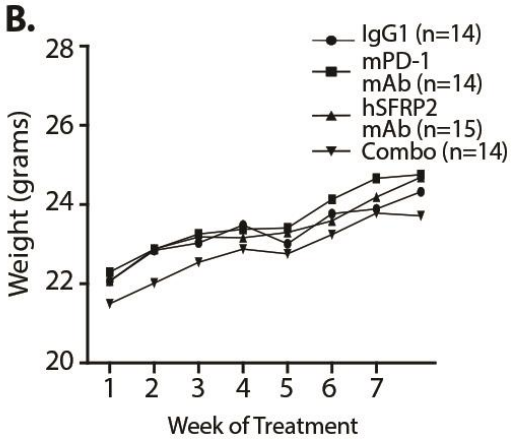
- IVT-8086, by antagonizing SFRP2, has been shown to improve efficacy of PD-1 inhibitors in combination without off target toxicity
- **This pattern of improved efficacy of IVT-8086 in combination with PD-1 inhibitors should occur across most other cancers**

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

Monotherapy and Combination Therapy Inhibits Osteosarcoma Lung Metastases in 2nd 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

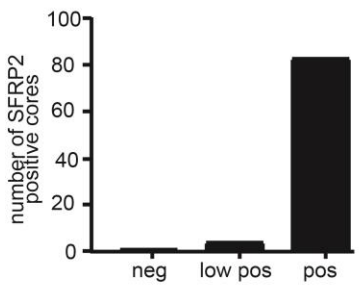
No evidence of toxicity as noted by no change in body weights in any groups during the study

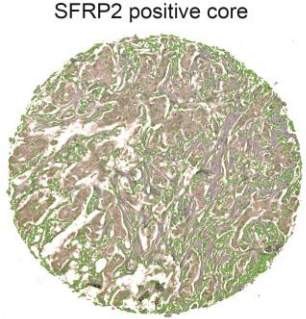
Nasarre, P. et al. Overcoming PD-1 Inhibitor Resistance with a Monoclonal Antibody to Secreted Frizzled- Related Protein 2 in Metastatic Osteosarcoma. Cancers 2021, 13, 2696.

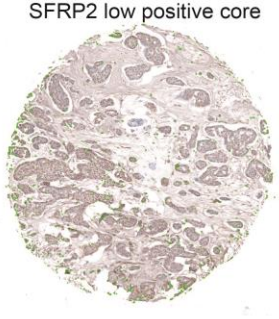
Could Combination IVT 8086 with Check Point Inhibition be Additive/Synergistic in TNBC?

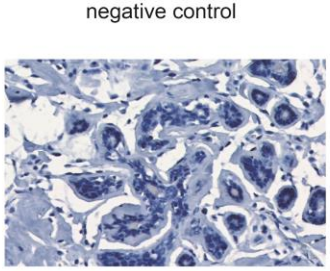
No studies have demonstrated whether CD38 is expressed in TNBC

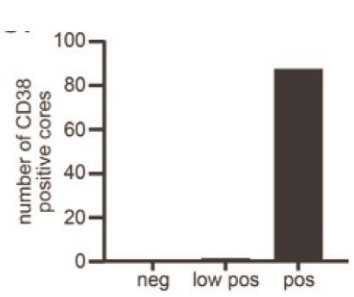
SFRP2 and CD38 are Expressed in Human Triple Negative Breast Cancer (TNBC)

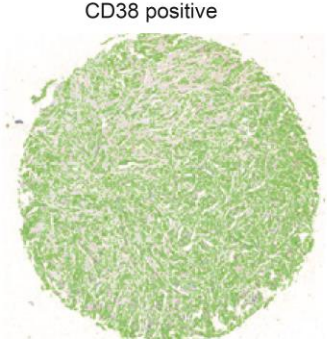


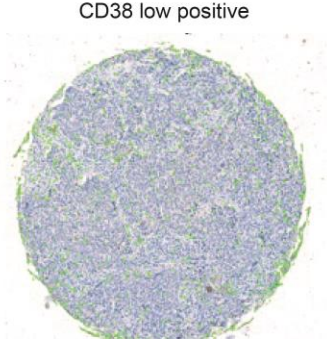


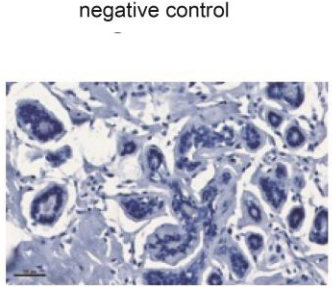






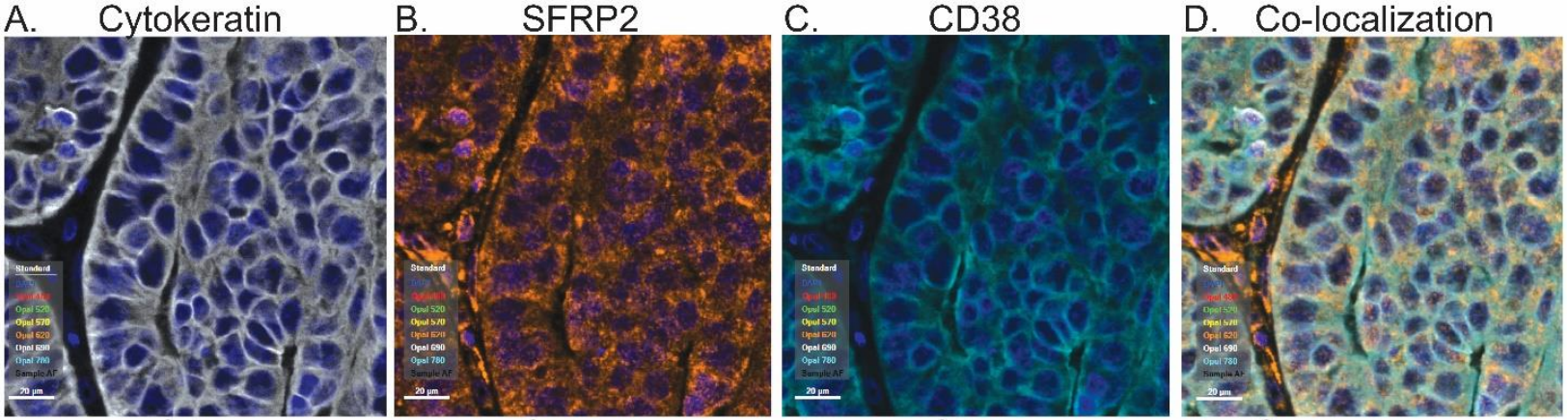


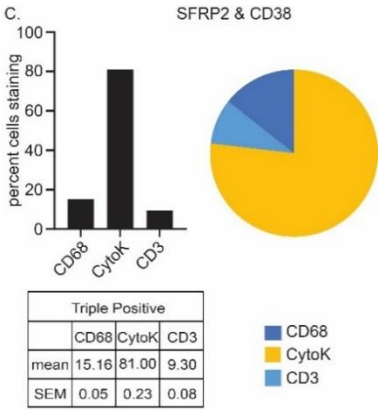




- Tissue microarray with 88 Formalin-Fixed Paraffin Embedded (FFPE) Tissue TNBC Cores
- Immunohistochemistry (IHC) for SFRP2 and CD38 show both are abundantly expressed in TNBC

SFRP2 and CD38 Co-localize in Breast Tumors





Triple Positive			
	CD68	CytoK	CD3
mean	15.16	81.00	9.30
SEM	0.05	0.23	0.08

- 99% of CD38+ cells are SFRP2+
- CD38+/SFRP2+ in
  - 81% of tumor cells
  - 15% of macrophages
  - 9% of T-cells

Innova therapeutics

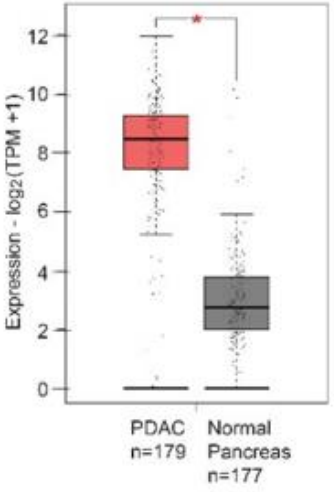
Background on KRAS and Pancreatic Ductal Adenocarcinoma (PDAC)

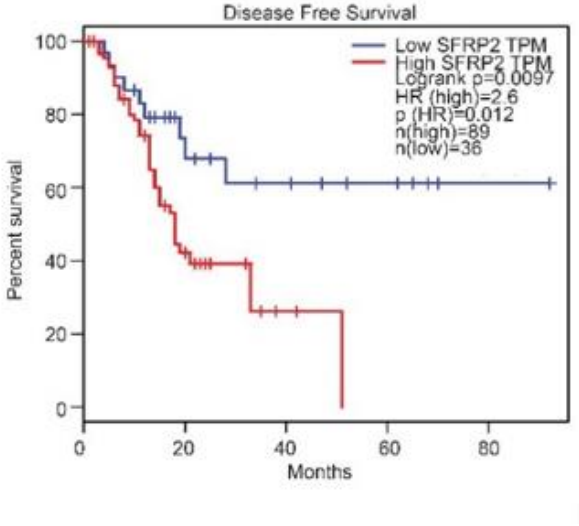
- Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal solid malignancies with increasing incidence.
  - The poor prognosis is due to the aggressive nature of the tumor, late detection, and the resistance to chemotherapy and radiotherapy.
  - The majority of patients (80-85%) at first diagnosis 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.





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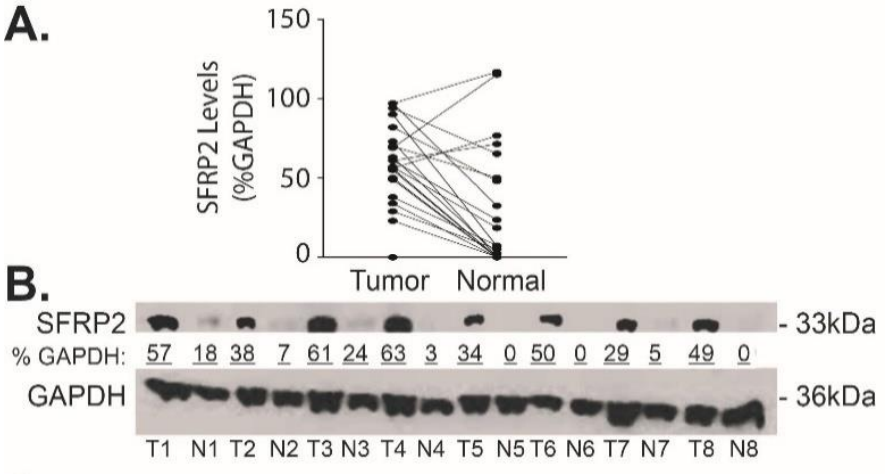
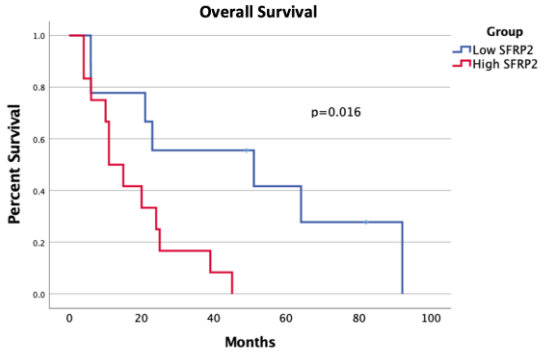
SFRP2 Protein Increased in PDAC and Not in Adjacent Normal Tissue
SFRP2 is an Independent Prognostic Factor for Poor Prognosis

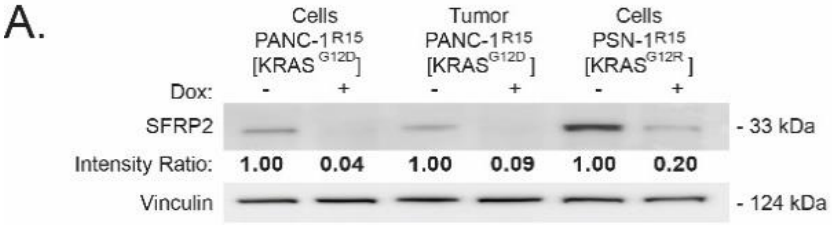


(A) Western blot comparing the levels of SFRP2 between tumor tissue from patients and their normal adjacent pancreatic tissue.
(B) Representative western blot of tumor tissues (T) and their normal adjacent tissues (N).

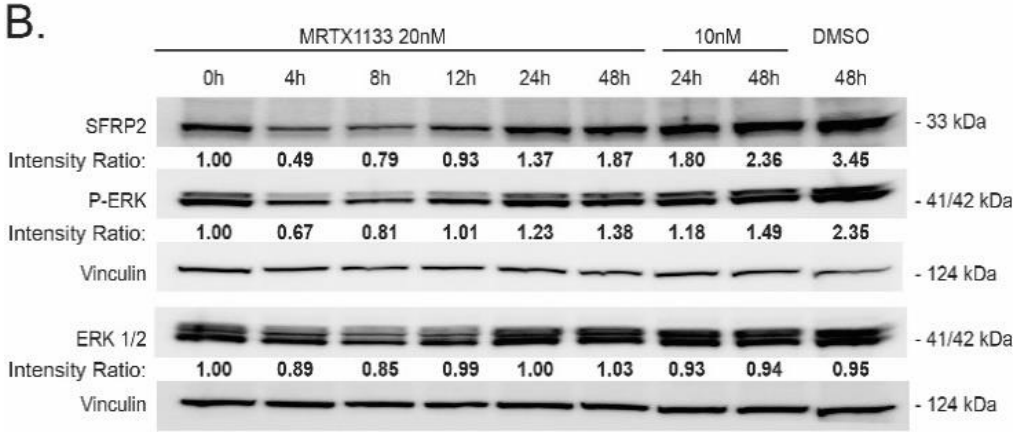
- In patients with Stage 1 and Stage 2 PDAC cancer undergoing pancreatic resection at Medical University of South Carolina (MUSC), SFRP2 protein was elevated compared to adjacent normal tissue.
- SFRP2 levels in tumors even in early stage PDAC correlated with outcome



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 SRFP2 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 $KRAS^{G12D}$ 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

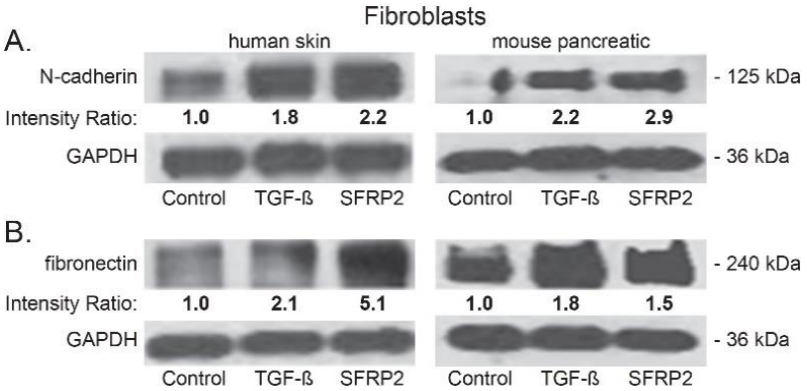
- Pancreatic cancer has the highest level of stroma (~80% of its mass) of any solid organ tumor which decreases the tumor vasculature and raises the interstitial pressure, shielding the tumor from chemotherapy and immune response

- 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

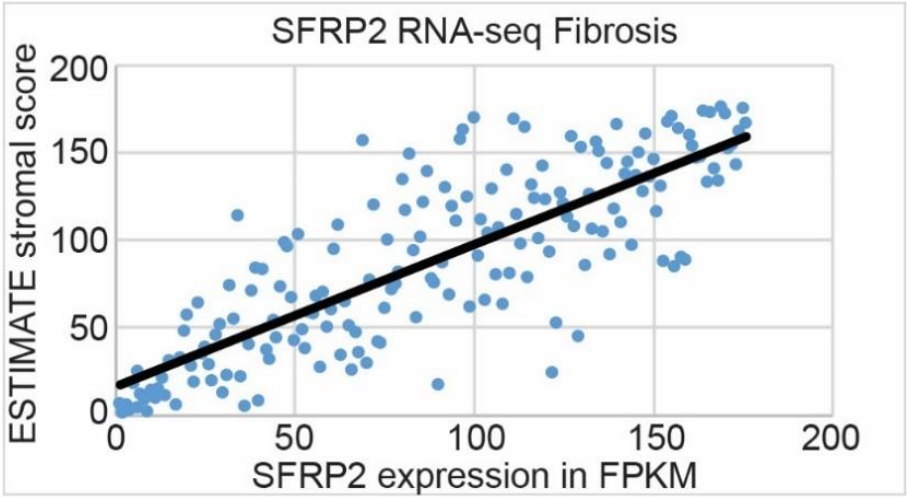
SFRP2 Induces Epithelial Mesenchymal Transformation in Fibroblasts



(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

Innova therapeutics

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 TGFβ 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 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

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

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 **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
- 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
- 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
- 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

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

GMP Manufacturing of mAb
- DS/DS Scale-up

IND Enabling Toxicology studies
- ELISA development
- 14-day range finding in rat
- MTD 10-day range finding monkey
- 28-day tox in rat and non-human primate with 28-day recovery
- Tissue cross reactivity in humans (done)

- Meet with FDA on development plans including osteosarcoma accelerated development strategy, file and open IND

Phase 1 Dose Escalation Study in pediatrics (OS) and adults with solid tumors, including sarcomas

Phase 1 Dose Escalation Study in combination with PD-1 inhibitor in patients with sarcoma, breast and pancreatic cancer

* Initiate and complete Phase 2 study **registrational study** in pediatric osteosarcoma (POS) – designed to support accelerated approval in POS and receipt of voucher

*Initiate and complete Phase 1B/2 Studies (Monotherapy) patients with breast cancer (including TNB), sarcomas, multiple myeloma, and pancreatic cancer with assessments including: PK assessment, core biopsy pre- and post-treatment with pathology, CT scans, Elisa assay for SFRP2 serum level measurements

*Initiate and complete Phase 1B/2 Studies (Combination Therapy) patients with breast cancer (including TNB), sarcomas, multiple myeloma, and pancreatic cancer with assessments including: PK assessment, core biopsy pre- and post-treatment with pathology, CT scans, Elisa assay for SFRP2 serum level measurements

**** With frequent CT scans (q 6-8 weeks) will be able to evaluate IVT-8086 treatment effect on tumors in patients early in the studies***