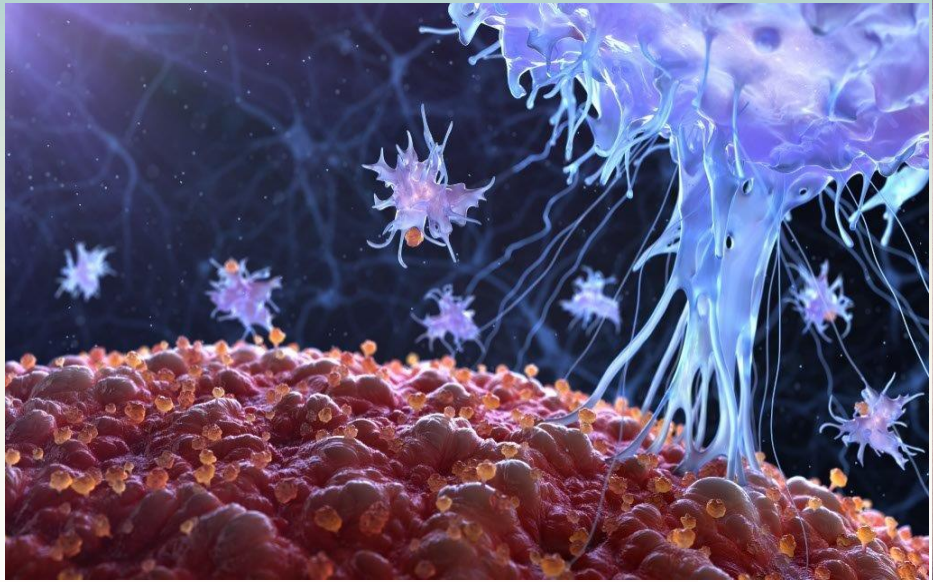
Improving Lives of Patients with Cancer



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-PD-(L)1 checkpoint inhibitors for cancers with high unmet need **(sarcomas (including osteosarcoma (OS)), pancreatic, multiple myeloma, and 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 2040**

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

Dr. Robert Ryan
CEO and Co-Founder

- 30 years of global drug development experience, including preclinical, clinical development, and regulatory affairs, across multiple therapeutic areas including 16+ years development of oncology therapeutics
- Senior pharmaceutical operational and management experience in small to large pharma/biotech organizations (Pfizer, Bristol-Myers, UCB, Atherogenics, Celtic), and CROs (Quintiles, PPD, INC Research)
- Direct development involvement resulting in approval of over 20 drug candidates across various therapeutic areas.

Nancy Klauber-DeMore, MD, FACS
Medical and Co-Founder

- Professor of Surgery, Medical Director of the Medical University of South Carolina (MUSC) Breast Center, and Program Director of the MD/PhD Program at MUSC. BMW Endowed Chair in Cancer Research, MUSC
- Program Director Developmental Cancer Therapeutics Hollings Cancer Center and MUSC Medical Scientist Training Program
- Surgical Oncology Fellowship at Memorial Sloan Kettering Hospital, and Cancer Research Fellowship at Harvard Medical School.

Dr. Ronald V. Nardi
Executive Vice President Development

- More than 35 years experience in drug discovery/development and regulatory affairs
- Operational and management R&D experience in large pharma organizations (Wyeth, Glaxo, Warner-Lambert) and small/medium sized companies including specialty pharma and start-up/biotechnology firms
- Broad range of R&D experience from therapeutic target identification to clinical drug development and regulatory registration filings in multiple therapeutic categories

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
- Past CFO and President / CEO for ARIES ALLIANCE Company with global operations in the U.S., France, UK, Canada, Russia, Singapore, China and Japan.
- Mr. Zimmer worked for Price Waterhouse Coopers in Auditing and Consulting, and brings experience with M&A and MBO transactions, Bank Financing, Capital Acquisitions, Site Selection and Incentive Plans, and Negotiations

Willistine Lenon
Executive Vice President, Clinical Operations

- Highly experienced Clinical Operations Executive with 20+ years in the field of clinical research, including senior roles at major CRO and pharmaceutical companies
- Extensive experience in a wide variety of key therapeutic areas: oncology, pulmonary/allergy, cardiovascular, genitourinary, dermatology, hematology, metabolic disorders, neurology, ophthalmology, analgesia and rheumatology
- Global operations experience including the US, Canada, Latin America, Europe, and Asia.

Steve Cole
Head of Business Development and Licensing

- Highly experienced Business Development/Licensing executive with 40+ years of global industry experience. Prior roles include senior positions at Abbott Laboratories, Vice President for Asia and Canada and a member of the International Executive Committee at G.D. Searle, and President at A.H. Robins, responsible for international operations.
- Steve Cole had direct involvement in the acquisition of Tolero Pharmaceuticals by Sumitomo Dainippon ($750m) as well as licensing deals for Lung Therapeutics, Akebia, MGI Pharma, etc.

…and a Renowned Scientific Advisory Board (SAB)

Nancy Klauber-DeMore, MD, FACS
Co-founder, BMW Endowed Chair in Cancer Research at Medical University of South Carolina (MUSC)

Dr. DeMore is Professor of Surgery, Medical Director of the MUSC Breast Center, and Program Director of the MD/PhD Program at MUSC. Dr. DeMore completed her Surgical Oncology Fellowship at Memorial Sloan Kettering Hospital, and Cancer Research Fellowship at Harvard Medical School. She is a practicing surgical oncologist with research interest in tumor angiogenesis and immunology.

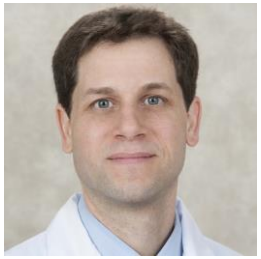
Cam Patterson, MD, MBA
Co-founder, Chancellor of the University of Arkansas for Medical Sciences (UAMS)

Prior to being named Chancellor at UAMS, Dr. Patterson was previously the Senior Vice President and Chief Operating Officer at New York Presbyterian Hospital/Weill-Cornell Medical Center in New York, from 2014-2018; and the Physician-in-Chief of the UNC Center for Heart and Vascular Care, the Chief of the Division of Cardiology, and the Director of the McAllister Heart Institute at the University of North Carolina at Chapel Hill from 2001-2014. Dr. Patterson research interests are in the areas of angiogenesis and vascular development, cardiac hypertrophy, protein quality control, and translational genomics and metabolomics.

Elizabeth Claire Dees, MD, MSc
Professor of Medicine, Division of Hematology and Oncology, UNC Hospital

Dr. Dees is a practicing medical oncologist, an active member of the UNC Breast Center, and the founding chair of the Developmental Therapeutics (Phase I trials) Working Group at UNC. She is the co-leader of the Clinical Research Program at UNC Lineberger. Dr. Dees completed her internship and residency in internal medicine at the Brigham and Women's Hospital in Boston and her medical oncology fellowship training at the Johns Hopkins Oncology Center where she worked with the Phase I trials group and the breast cancer program.

William D. Tap, MD
Chief, Sarcoma Medical Oncology Service, Memorial Sloan Kettering Cancer Center



Dr. Tap is the Chief of the Sarcoma Medical Oncology Service at Memorial Sloan Kettering Cancer Center in New York. He is a medical oncologist who specializes in the treatment of patients with soft tissue and bone sarcomas and the development of novel therapies in rare cancers and neoplasms. Bill's academic research interests are focused on understanding the genetic and molecular nuances of sarcoma with an emphasis on identifying and validating therapeutic targets, treatment biomarkers, and modeling drug resistance. Bill received his MD from Jefferson Medical College, was a resident in Internal Medicine at the Vanderbilt University Medical Center, and a fellow in Hematology and Medical Oncology at the UCLA Medical Center in Los Angeles, CA.

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Previous Team Success with Recent Company, Scioderm

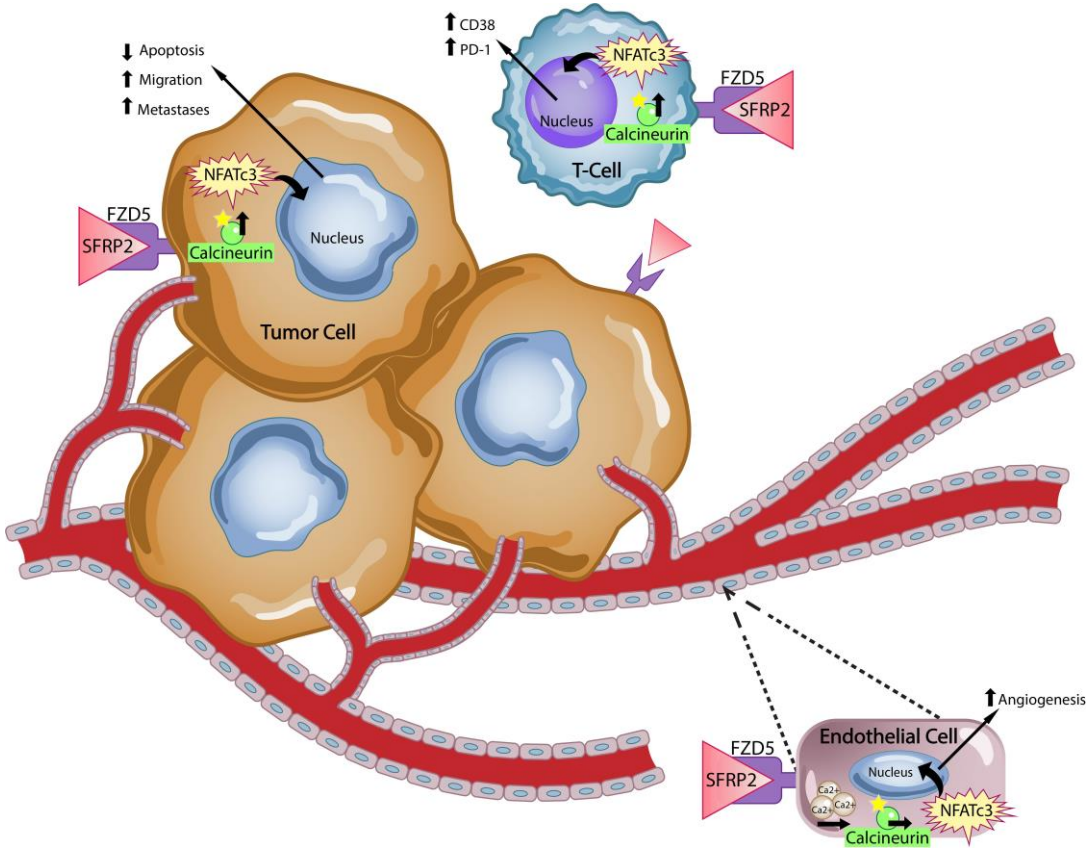
COMPANY ACCOLADES	DEVELOPMENT MILESTONES	SIGNIFICANT EXIT	ROBERT RYAN
First Biotech to receive "Breakthrough Therapy Designation" from FDA	Progressed program from Pre-IND to Phase 3 in less than 2 years	$22M total spend prior to merger with Amicus for deal totaling appr $957M	Selected as N.C. CEO of the Year for Life Sciences
Selected as one of the "Fierce Top 15" by FierceBiotech, considered as one of the most promising emerging companies in the biotech industry	Agreed PIP in Europe resulting in 12 years total exclusivity	**4th largest venture capital (VC) backed exit of 2015 in biotech/pharmaceutical space, 9th largest exit across all sectors.**	Selected as CEO of the Year for Biotechs by Financial Times
	Identical development program through commercialization with FDA and EMEA, with waiving of all long-term toxicology	Multiple termsheets from Japan for in-licensing within 6 months of discussions	

>$1B Commercial Opportunity

Innova therapeutics

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



Klauber-DeMore Lab Pubs, Bhati, R. et. al., Am J Pathol, 2008

Courtwright, A. et al, Cancer Research , 2009

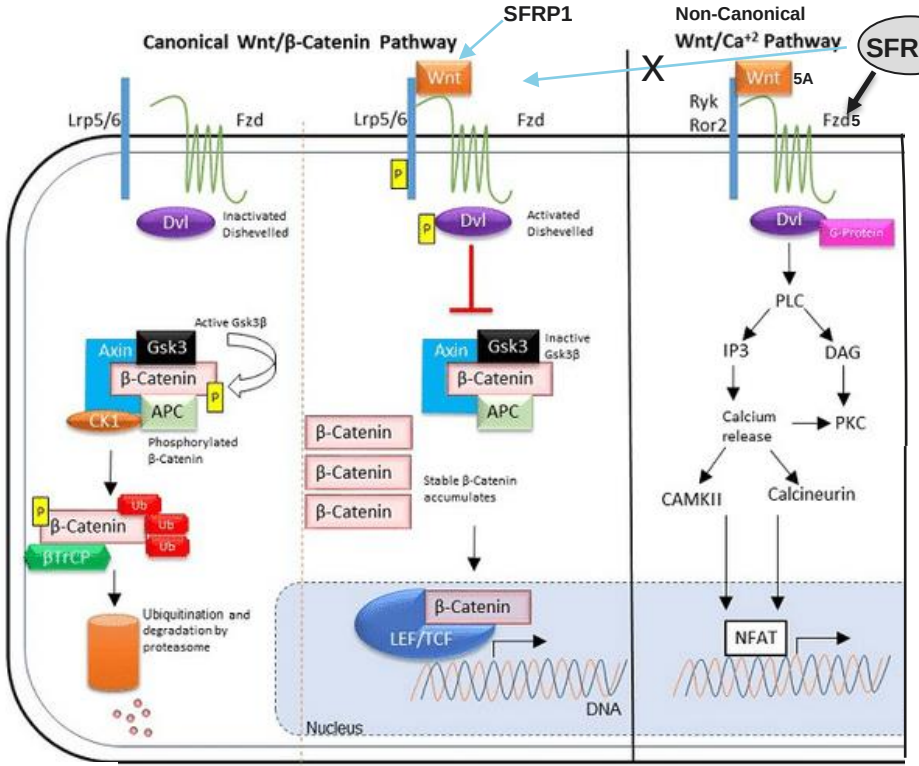
Siamakpour-Reihani, R. et al. Plos One, 2011

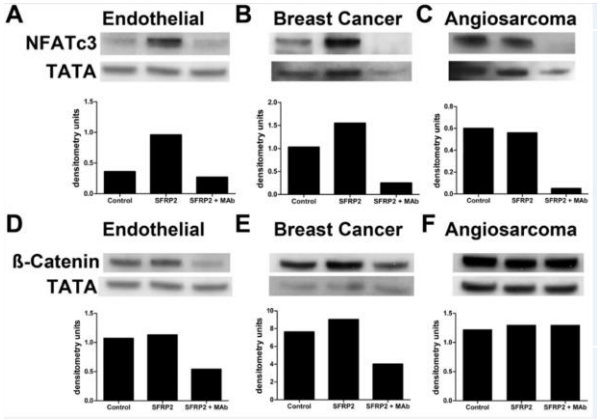
Fontenot, E. et. al., Mol Cancer Ther., 2013 Tsuruta, JK Plos One, 2014, Tsuruta, JK Plos One, 2017

Peterson, YK et. Al., Angiogenesis, 2017

SFRP2 Targeted Antagonism of Non-Canonical Wnt/Ca^{+2} Pathway

Key in Terms of Efficacy and Safety in Treating Cancer





* SFRP2 stimulates NFATc3, but does not stimulate β-catenin

* Inhibition of SFRP2 blocks NFATc3, and does not stimulate β-catenin

- SFRP2 selectively binds directly to the frizzled 5 (FZD5) receptor and activates the calcineurin/NFATc3 pathway resulting in stimulation of tumor growth
  - **Antagonism of SFRP2 causes a decrease in angiogenesis, tumor growth, migration, metastasis, T-cell exhaustion markers (PD-1, CD38), and an increase in tumor apoptosis.**
  - SFRP2 **<u>does not</u>** interact with the canonical β-catenin pathway

* Peterson YK, et al. Angiogenesis. 2017;20(4):615-28.

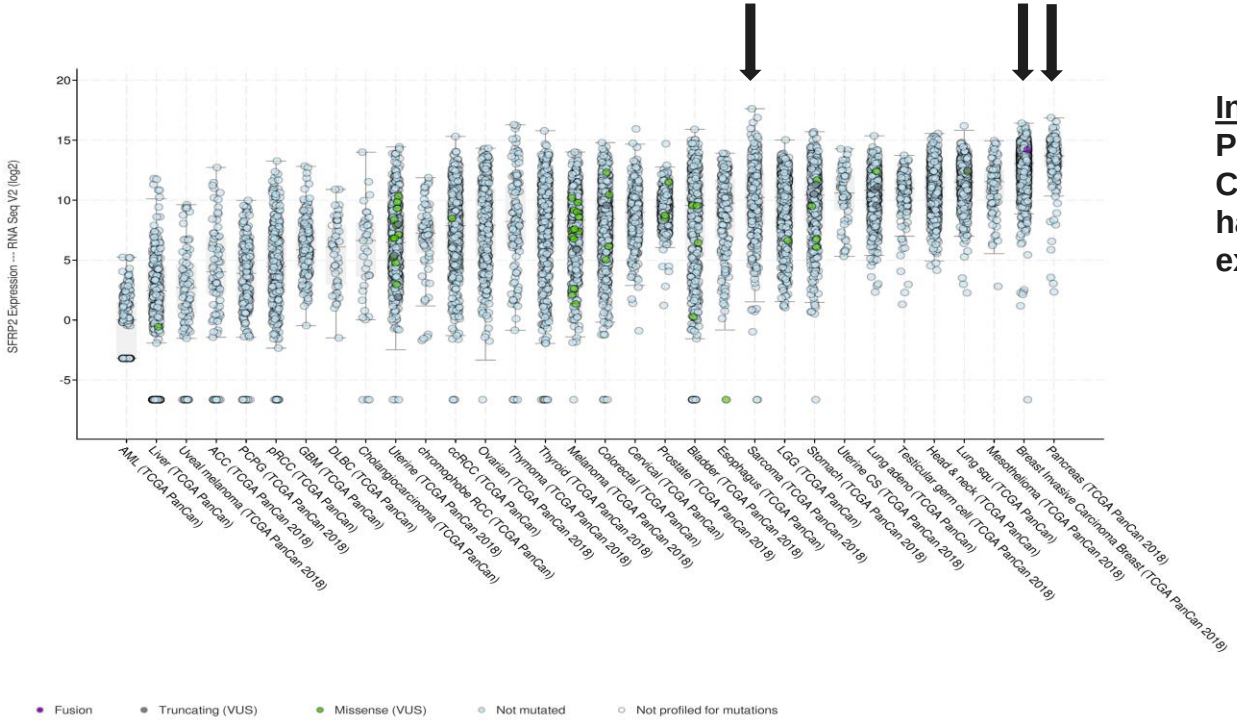
* Fontenot E, et al. Mol Cancer Ther. 2013 May;12(5):685-95.

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

TCGA Data Evaluating SFRP2 mRNA Expression Across Human Tumors



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

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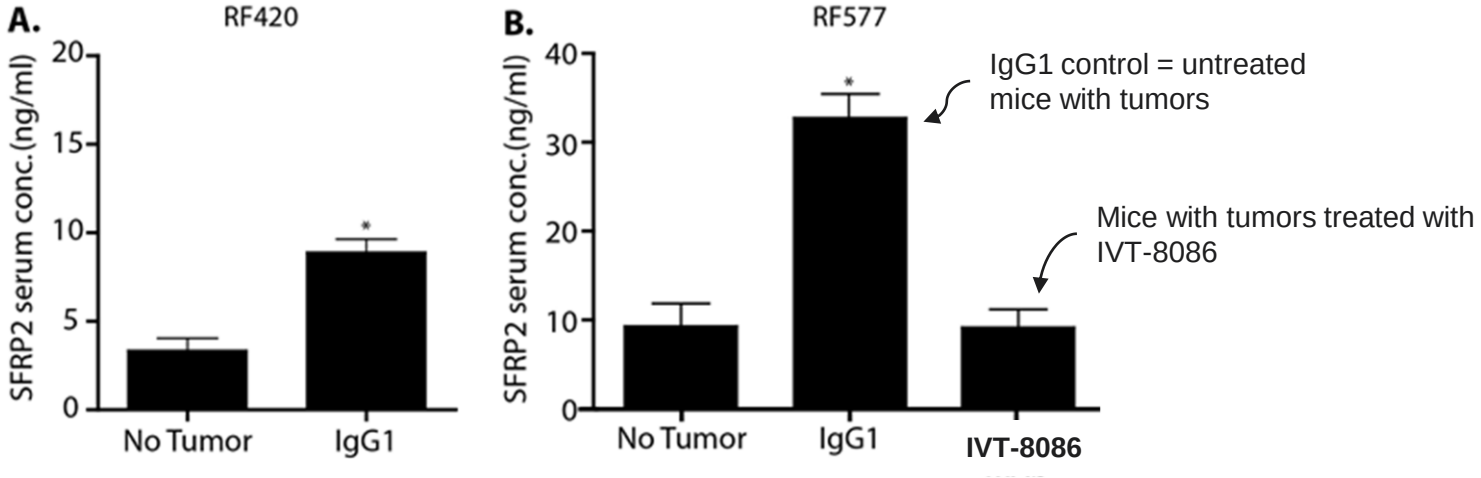
SFRP2 Levels Elevated in Mice with Osteosarcoma and Reduced with IVT-8086 Treatment



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).

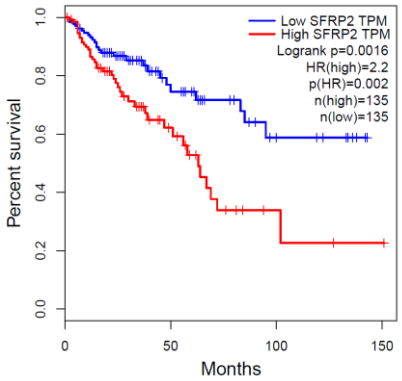
B) B) ELISA was used to compare the serum levels of SFRP2 in all treatment groups of the C57/BL6 mice with metastatic RF577 OS and C57/BL6 mice without tumors. The serum level of SFRP2 was significantly higher in the IgG1 group compared to no tumor (*p<0.01). The serum level of SFRP2 was decreased in the IVT-8086 treatment group (n=12) compared to IgG1 (control) 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.

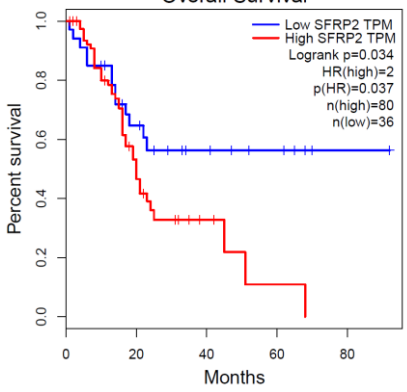
SFRP2 mRNA Expression Correlates with Survival in Cancer Patients

TCGA Data Evaluating SFRP2 mRNA Expression Across Human Tumors

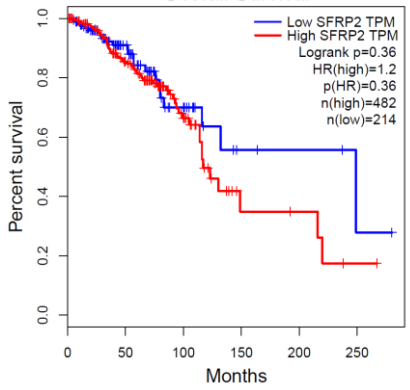
Colon Adenocarcinoma



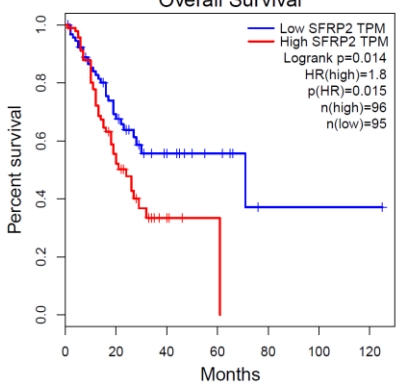
Pancreatic Adenocarcinoma



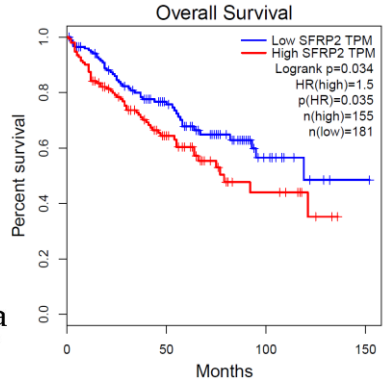
Breast Invasive Carcinoma



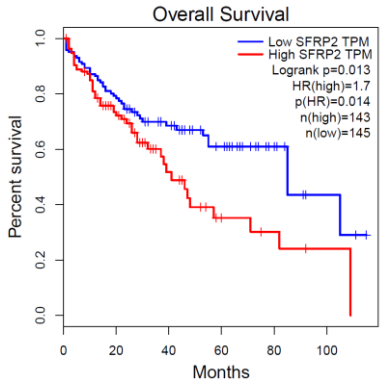
Stomach Adenocarcinoma



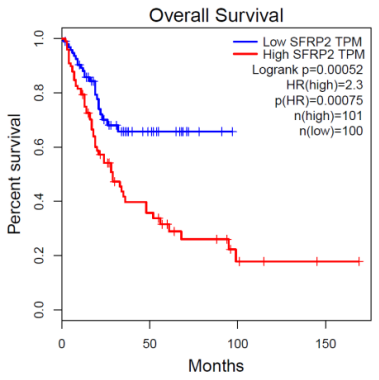
Renal Clear Cell Carcinoma



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

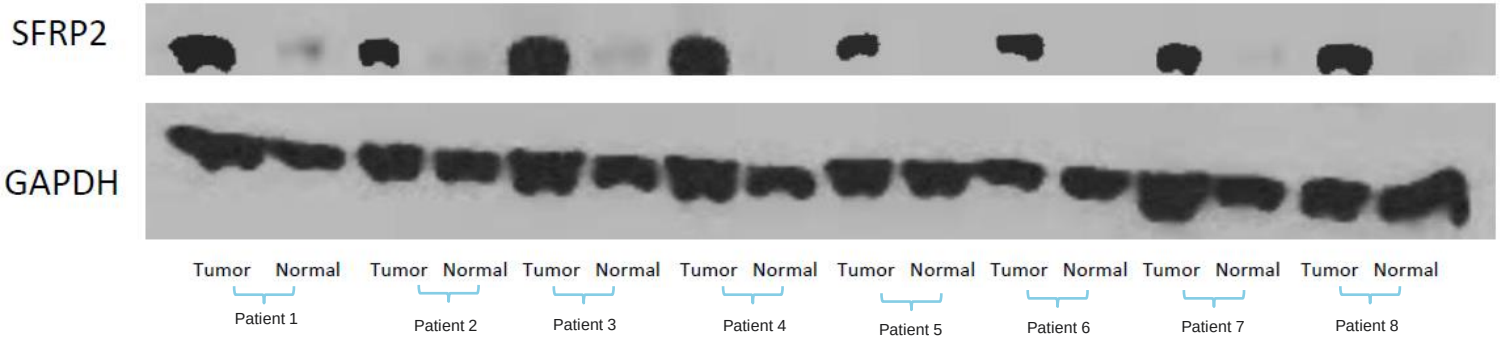
Tang, Z. et al. (2017) GEPIA: a web server for cancer and normal gene expression profiling and interactive analyses. Nucleic Acids Res, 10.1093/nar/gkx247.

Innova therapeutics

SFRP2 Protein Levels Correlate with Survival in Pancreatic Cancer Patients

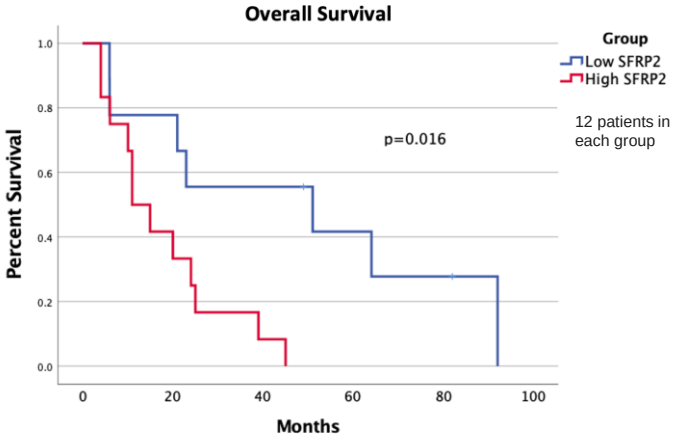
SFRP2 is an independent prognostic factor for poor prognosis

Patient Pancreatic Tumors with Matching Normal Adjacent Pancreatic Tissue



Medical University of South Carolina (MUSC) Tumor Bank samples

Stage I-III patients

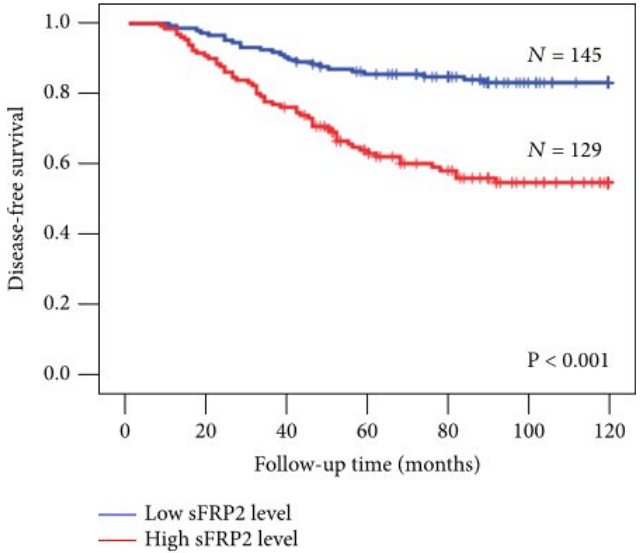


Demore Unpublished data

Innova therapeutics

SFRP2 is Associated with Disease Progression and Aggressiveness in Breast Cancer Patients

- SFRP2 plasma 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

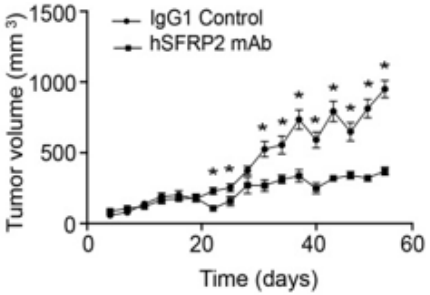


Kaplan-Meier survival curves of breast cancer patients. Progression-free survival rate of breast cancer patients with high (>58 ng/mL) and low (≤58 ng/mL) serum SFRP2 levels.

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.

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

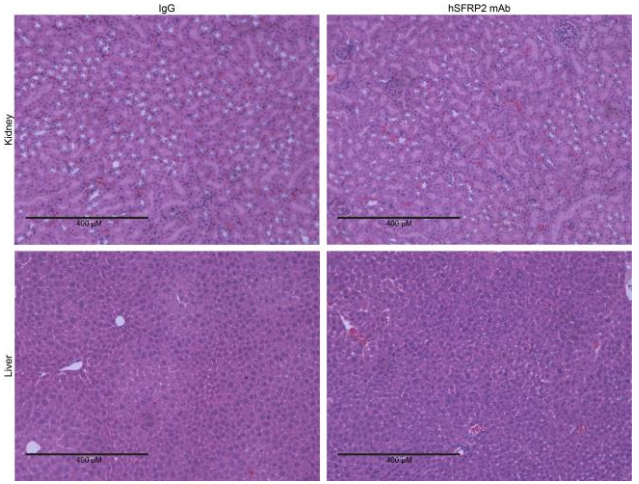
Metaplastic Triple Negative Breast (Hs578t)
CHEMORESISTANT



*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.

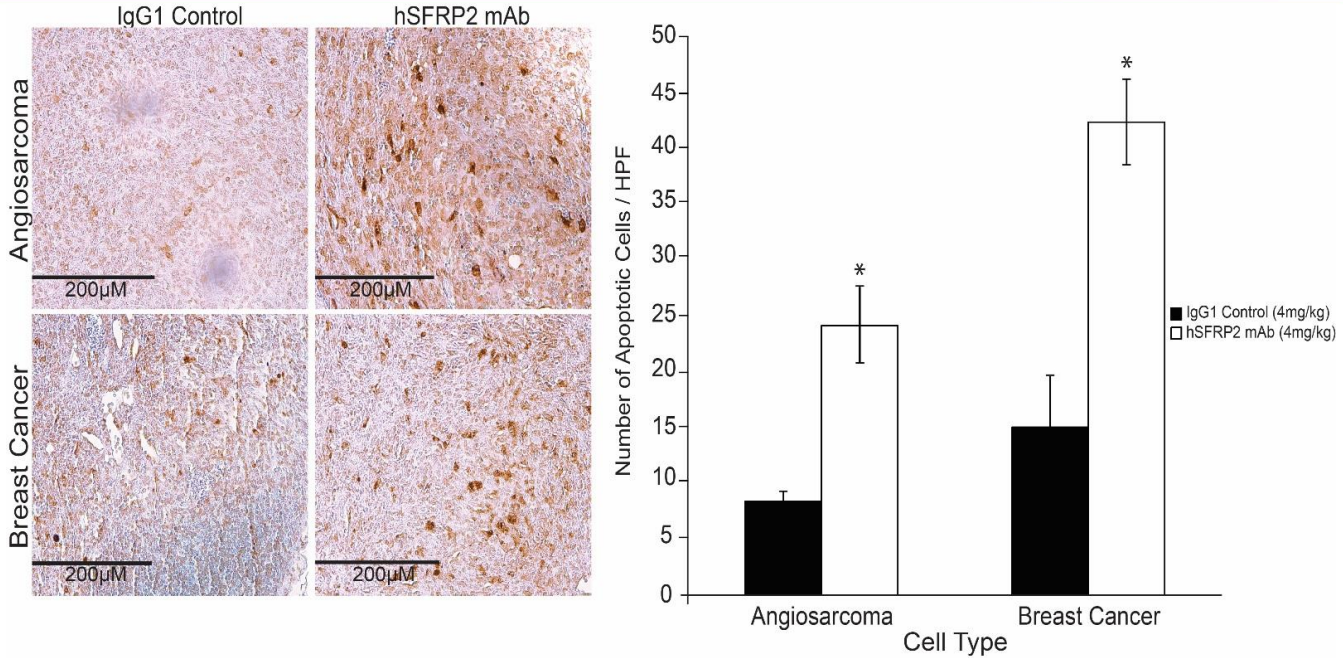


There were No Histological Changes in the Liver and Kidneys Following Multiple Dosing Administration at 4 times the Efficacious Dose (20 mg/kg) of IVT-8086 in Mice Injected with Angiosarcoma Cells

Mice injected with SVR angiosarcoma cells were treated with hSFRP2 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.

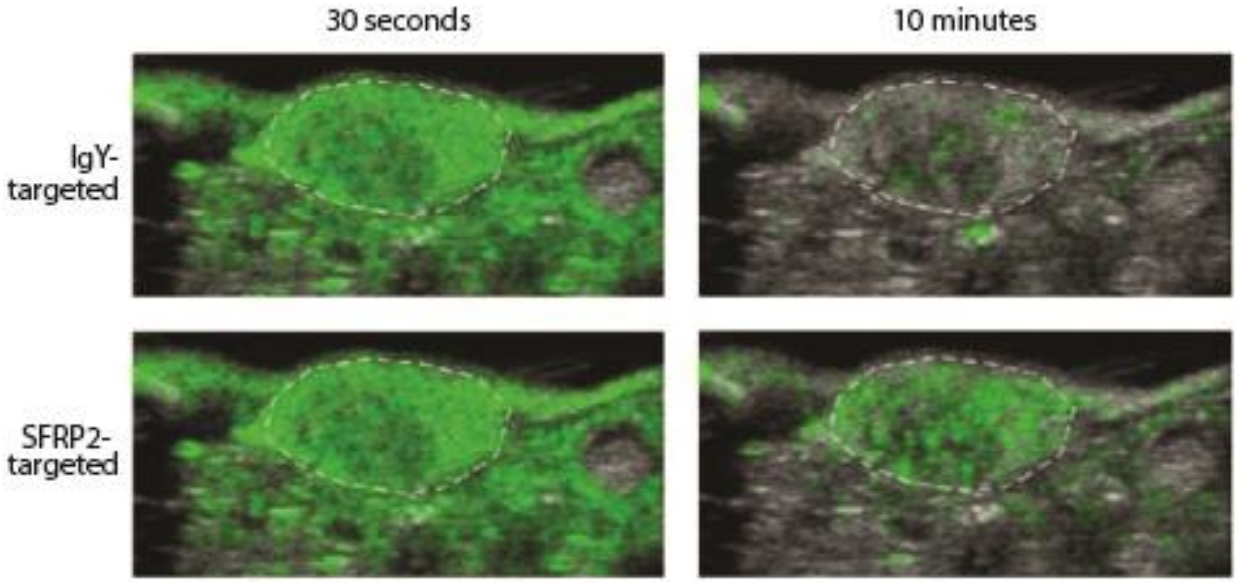
IVT-8086 Increases *in vivo* Tumor Apoptosis



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). *:$p \leq 0.05$.

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

SFRP2 Antibody Microbubble Contrast Agent Redistributes Rapidly to Tumor From Systemic Circulation



Ultrasound molecular imaging of angiosarcoma in animal receiving SFRP2-targeted and control IgY-targeted contrast was assessed after bolus injective via the tail vein.

A white dashed line outlines tumors. The contrast-specific signal (green) was superimposed over the b-mode image (grey). At 30 seconds, average video pixel intensity was similar between control and SFRP2-targeted contrast. The contrast-specific video intensity was retained in tumors at much higher levels when using the SFRP2-targeted contrast compared to the IgY-targeted contrast.

Tsuruta,JK, et al. PLoSONE 12(3):e0174281.

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*[1]
- Knockdown of SFRP2 within metastatic human and mouse OS cells demonstrated decreased cell migration and invasion ability *in vitro*[1]
- Strong SFRP2 expression in OS patient samples correlates with poor survival[2]
- SFRP2 overexpression suppresses normal osteoblast differentiation, promotes OS features, and facilitates angiogenesis via autocrine and paracrine mechanisms[2]

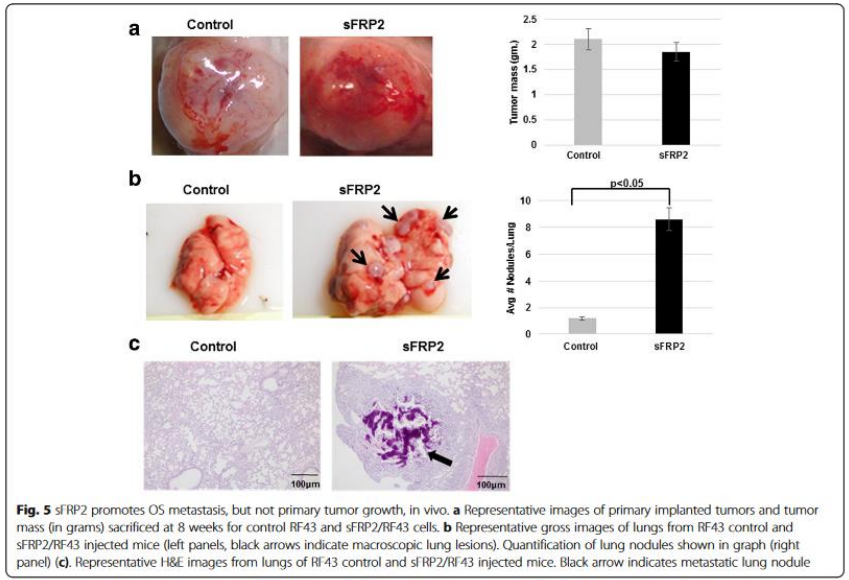
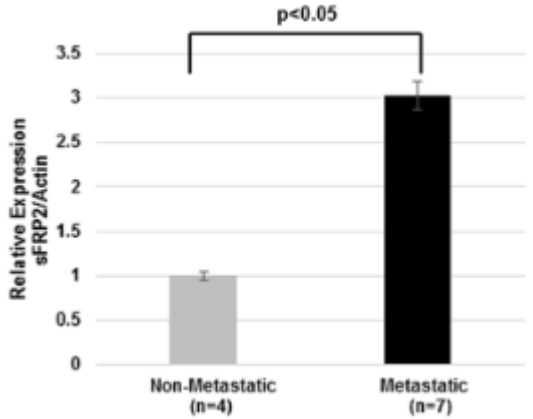


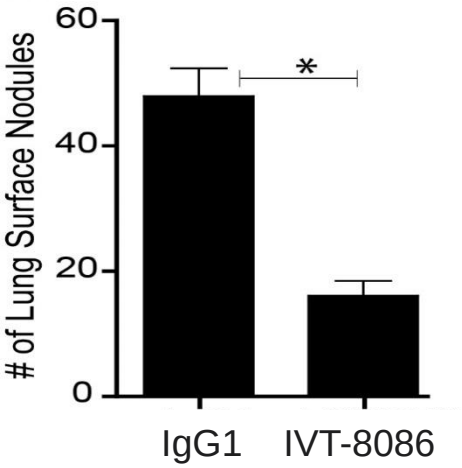
Fig. 5 sFRP2 promotes OS metastasis, but not primary tumor growth, in vivo. **a** Representative images of primary implanted tumors and tumor mass (in grams) sacrificed at 8 weeks for control RF43 and sFRP2/RF43 cells. **b** Representative gross images of lungs from RF43 control and sFRP2/RF43 injected mice (left panels, black arrows indicate macroscopic lung lesions). Quantification of lung nodules shown in graph (right panel) (**c**). Representative H&E images from lungs of RF43 control and sFRP2/RF43 injected mice. Black arrow indicates metastatic lung nodule



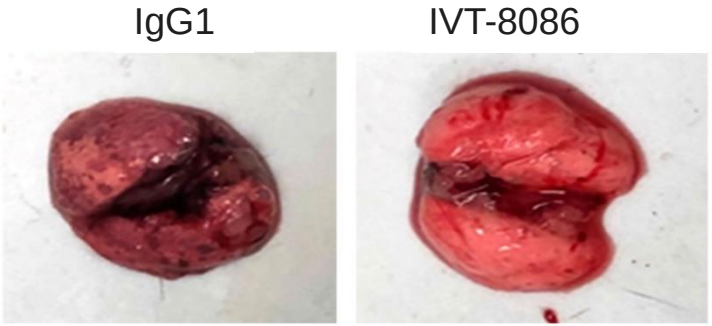
qPCR analysis comparing expression of SFRP2 in metastatic primary human osteosarcoma tumor tissue to non-metastatic tumor

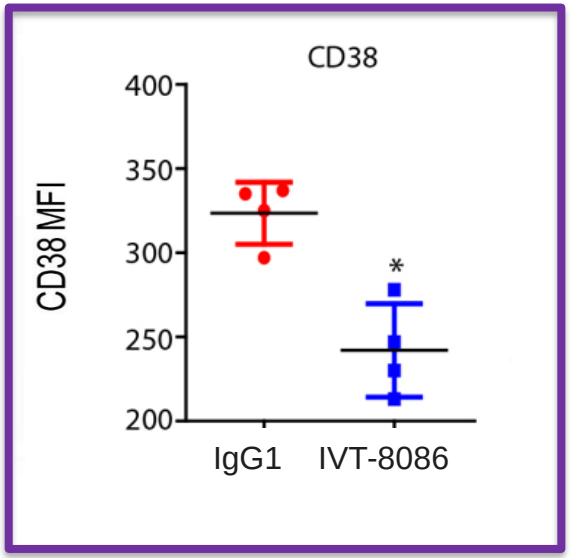
1. *Techavichit P, et al.BMC Cancer. 2016 Nov 8;16(1):869.*
2. *Kim H, et al. Proc Natl Acad Sci U S A. 2018;115(47)*

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



*p≤0.000, n=12

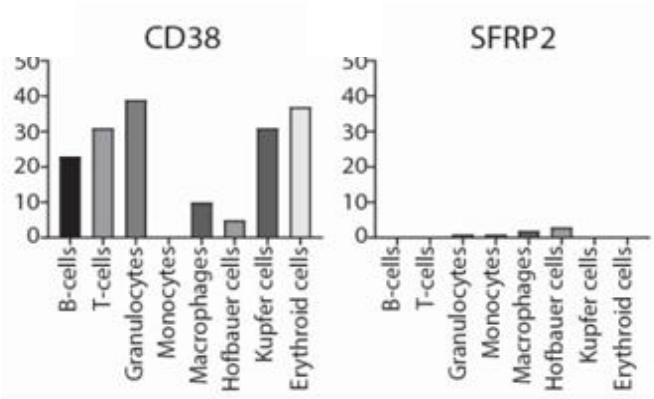




*p≤0.02

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.

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 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

Targeting SFRP2 should specifically inhibit CD38 only in cells that express SFRP2 restricted to the tumor and tumor microenvironment

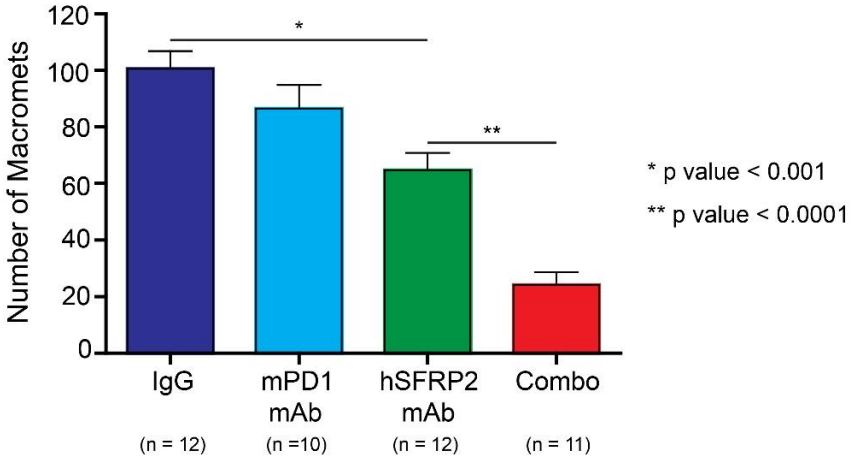
- Would expect an inhibitor of SFRP2 to improve efficacy of PD-1 inhibitors without off target toxicity

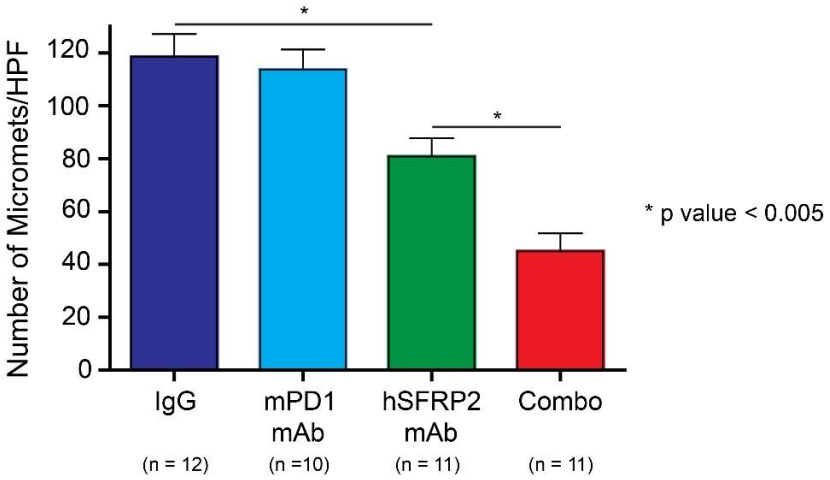
IVT-8086 reduces CD38 and improves efficacy of PD-1 inhibitors, with no observed toxicity

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

Innova therapeutics

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

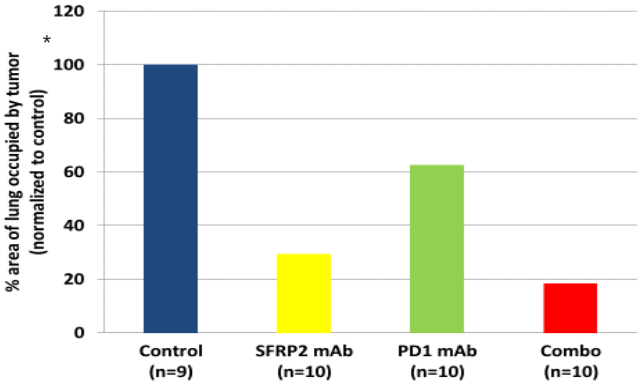


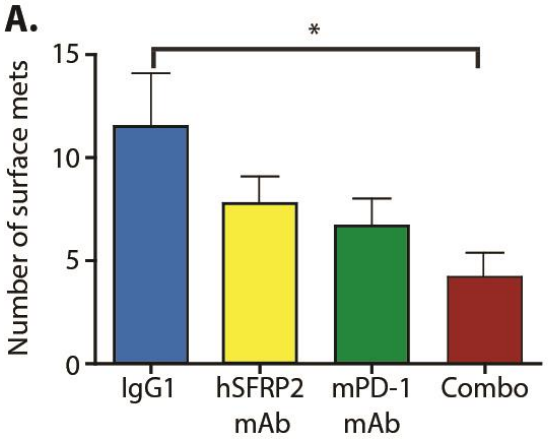


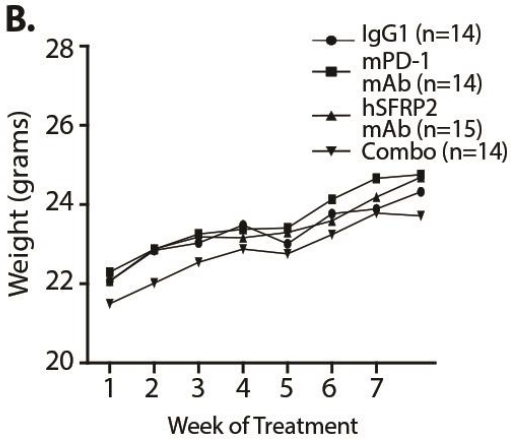
RF420 mouse osteosarcoma cells were injected in the tail vein of C57BL/6 mice. Starting on day 7 mice were treated with either IgG1 control (Xolair) 4 mg/kg iv weekly, or mouse PD-1 ab (200ug/mouse) every 3 days, or IVT-8086 4 mg/kg iv every 3 days, or the combination of both antibodies every 3 days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

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.

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

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

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.

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 its 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-,Sarcoma%20Drugs%20Market%20Size%20Worth,By%202023%20%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

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

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.**

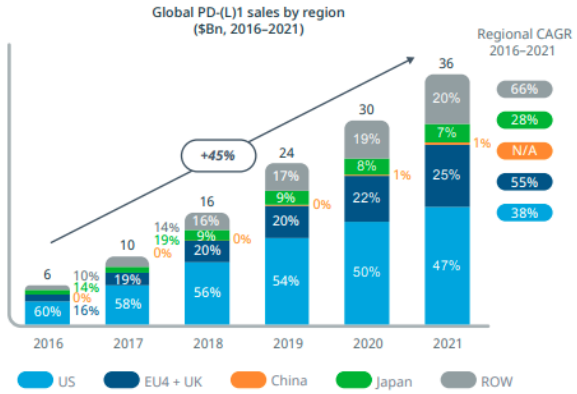
Sources:
https://www.gminsights.com/industry-analysis/monoclonal-antibodies-market?gclid=EAIaIQobChMI9v-4mMSM-QIV-ciUCR3M8wT-EAAYAiAAEgISv_D_BwE
https://www.globenewswire.com/en/news-release/2022/05/23/2448585/0/en/Monoclonal-Antibodies-Market-Size-to-Hit-US-524-68-Bn-By-2030.html#:~:text=The%20global%20monoclonal%20antibodies%20market,12.8%25%20from%202022%20to%202030
https://www.prnewswire.com/news-releases/cancer-monoclonal-antibodies-market-worth-159-7-billion-by-2030-grand-view-research-inc-301589238.html

PD-1 / PD-L1 Inhibitor Market: (current market size approx. $36B)

- **PD-1 inhibitors are the most commonly used cancer therapeutics, and are approved for treating 17 types of cancer.** Figure 1 depicts the fast growth of these cancer therapeutics with the market estimated to reach **$58 billion globally by 2025**.
- **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:
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

Figure 1: The global PD-(L)1 inhibitor market has enjoyed fast growth



IVT-8086 - An Exciting Novel Anticancer Therapy Targeting Secreted Frizzled Related Protein 2 (SFRP2)

- SFRP2 is a novel therapeutic target for multiple cancers affecting both primary tumor and metastatic disease
  - Multiple tumor types secrete SFRP2 in tumor cells, endothelial cells, and activated T-cells.
- Lead mAb, IVT-8086, has been shown to **directly antagonize SFRP2 resulting in selectively blocking the non-canonical Wnt/Ca2+ pathway** which significantly reduces tumor growth across multiple cancer
- Multi-faceted mechanism with inhibition of SFRP2 in cancer including:
  - Reduced tumor growth (primary and metastatic disease), including increased apoptosis of tumor cells
  - Rescues T Cell dysfunction including T Cell exhaustion, impacting expression of PD-1 and CD-38
  - Reduced angiogenesis, reduced migration and metastasis
  - IVT-8086 treatment reduces SFRP2 levels
- IVT-8086 monotherapy and combination therapy (with PD-1 mAb) has demonstrated significant efficacy (with no adverse safety effects) in multiple animal models implanted with human xenografts:
  - Results comparable in Human xenograft (immunodeficient) and Mouse syngeneic (immunocompetent) models both in primary tumor and metastatic disease
- SFRP2 has been validated as an important molecular target in human cancers which has been shown to correlate with patient outcome including overall survival across multiple cancers:
  - SFRP2 levels in plasma across all types of breast cancer were positively associated as an independent prognostic factor for tumor size, lymph node metastases, and poor prognosis including progression-free survival.
  - High expression levels of SFRP2 in osteosarcoma patients correlated with poor survival
  - SFRP2 is a secreted protein that can be measured in the blood of cancer patients
    - Development of companion diagnostic as a potential prognostic and predictive biomarker
- Clearly defined regulatory path
  - Broad therapeutic opportunities across multiple solid and hematological tumors including **fast regulatory approval timeline for Osteosarcoma, which was granted both Orphan designation and Rare Pediatric Disease (RPD) designation by the FDA with opportunity to obtain a Priority Review voucher (value range $80-350M)**