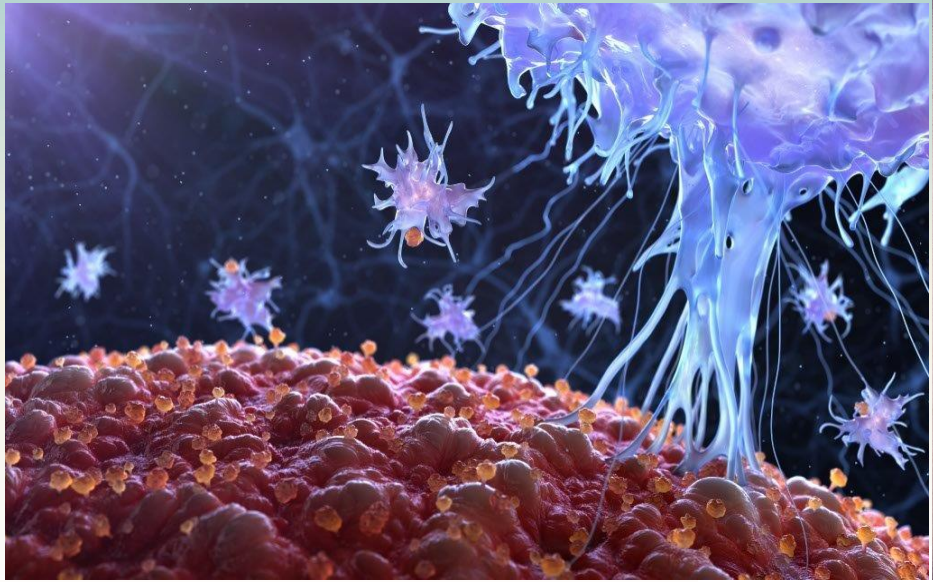
Improving Lives of Patients with Cancer



Innova therapeutics

Investment Highlights: IVT-8086 - An Exciting Novel Anticancer Therapy

Monoclonal Antibody (mAb) Platform Selectively Targeting Secreted Frizzled-Related Protein-2 (SFRP2), A Novel Anticancer Therapeutic Target Expressed Across Most Solid Cancers

Multi-faceted mechanism with inhibition of Secreted Frizzled Related Protein 2 (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, tumor cell migration and metastasis

➢ Lead mAb, 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**

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

➢ **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 $80-350M)**

➢ Progress lead mAb (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 for cancers with high unmet need (sarcomas (including osteosarcoma (OS)), pancreatic and triple negative breast cancer), and in combination with anti-PD-(L)1 checkpoint inhibitors

➢ Composition of matter patent issued, in addition to filed new composition of matter and PCT combination patents

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

Leadership Team

Dr. Robert Ryan
President and Chief Executive Officer

Dr. Doug Testa
Head of CMC

Willistine Lenon
Executive Vice President of Clinical Operations

Steve Cole
Head of Business Development and Licensing including Japan

Dr. Ron Nardi
Executive Vice President Development

Heather Howard
Office Manager

Key Consultants

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

Cam Patterson, MD, MBA
Medical consulting Co-founder

Chris Christoffersen
Previous Co-founder and Chairman of Board, Scioderm

…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.

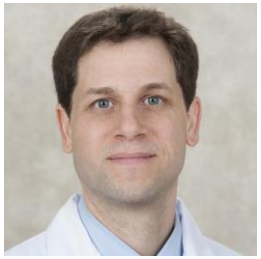
Cam Patterson, MD, MBA
Co-founder, Chancellor of the University of Arkansas for Medical Sciences (UAMS)

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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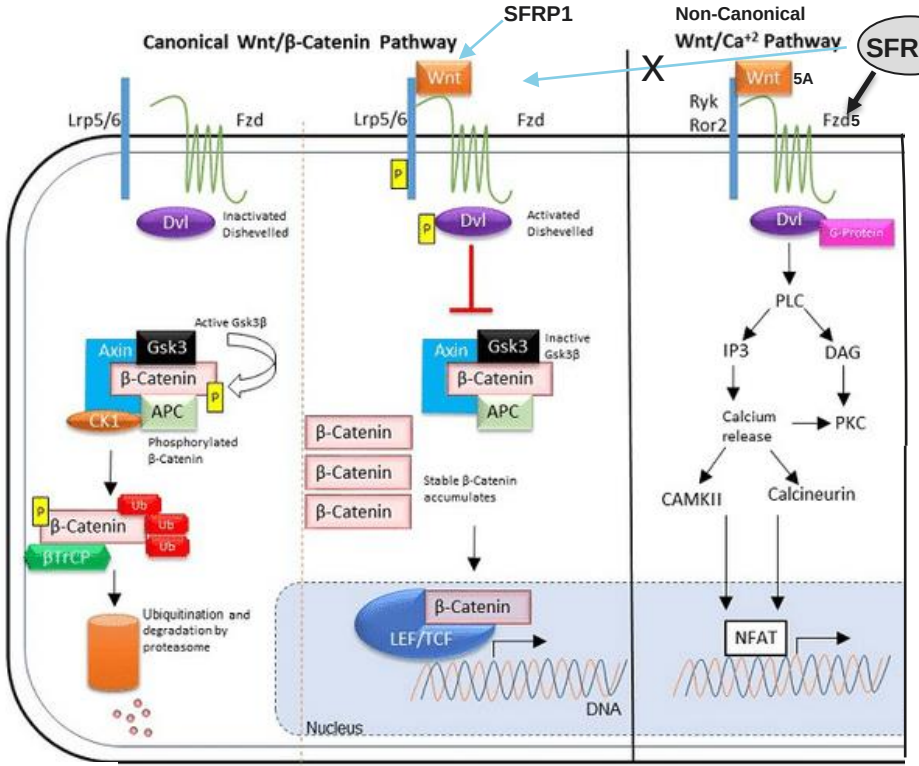
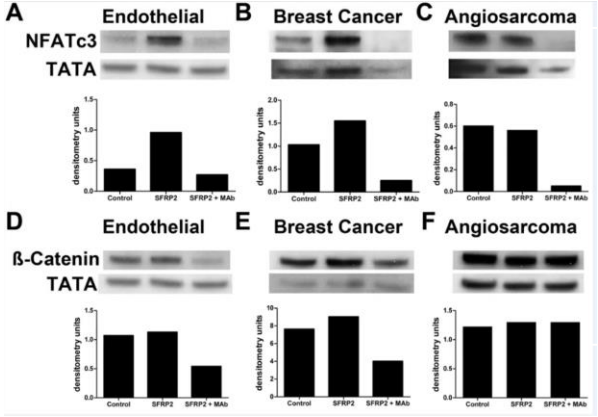
Multi-faceted Mechanism of Action

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

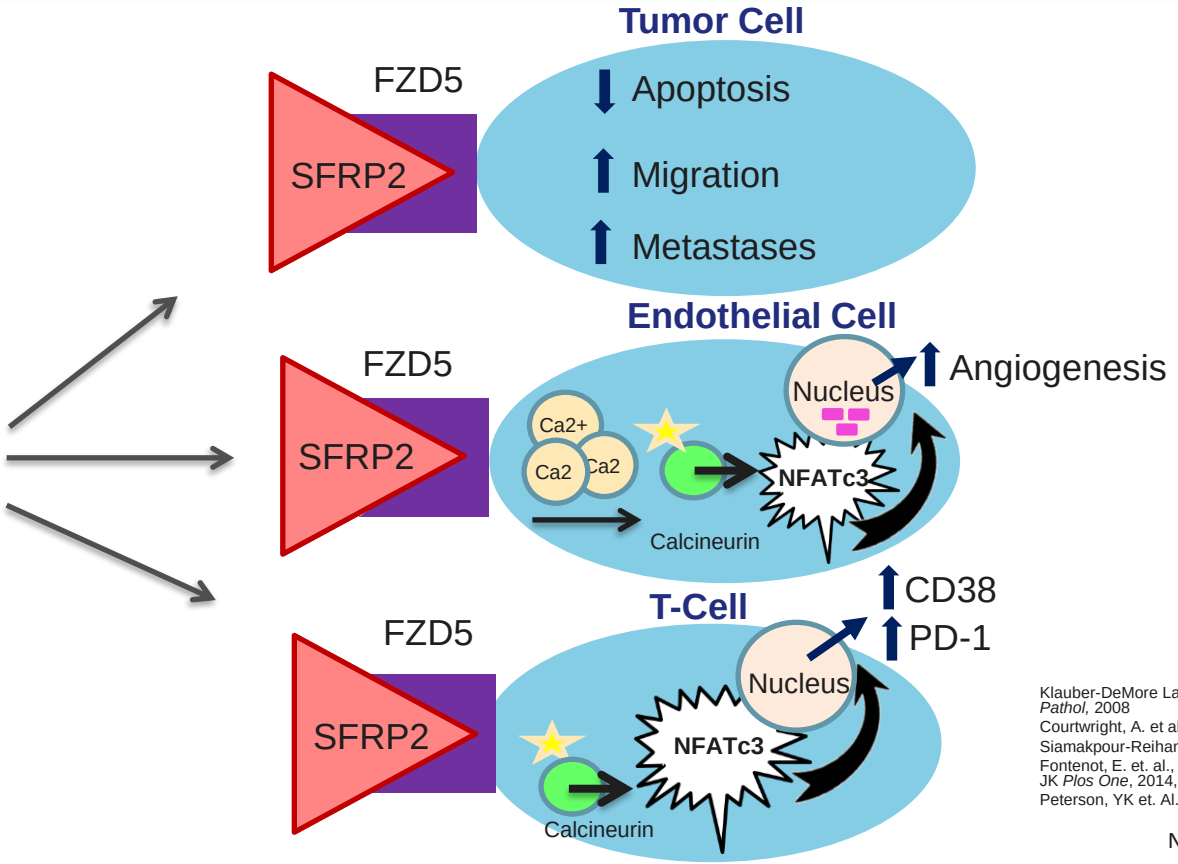
- SFRP2 selectively binds directly to the frizzled 5 (FZD5) receptor and activates the calcineurin/NFATc3 pathway resulting in stimulation of tumor growth
  - **Antagonism of SFRP2 causes a decrease in angiogenesis, tumor growth, migration, metastasis, T-cell exhaustion markers (PD-1, CD38), and an increase 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 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

- **Multiple tumor types secrete SFRP2 In endothelial cells, tumor cells, and T-cells.**
- SFRP2 binds to FZD5 and activates the calcineurin/NFATc3 pathway, translocating NFATc3 to nucleus. This causes an increase in angiogenesis, tumor growth, migration, metastasis, T-cell exhaustion markers (PD-1, CD38), and a decrease in tumor apoptosis.
- SFRP2 also activates NFATc3 in T-cells and is associated with increases in PD-1 and CD38.



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

Why is Reduction in PD-1 and CD38 Significant in Treating Cancer?

- Resistance to PD-1 inhibitors has been shown to be associated **with increased CD38 expression**
  - SFRP2 which is expressed in tumors, tumor endothelium, and tumor-infiltrating lymphocytes (tils), regulates NFATc3, which in turn regulates CD38
  - **SFRP2 antagonism reduces CD38 and improves efficacy of PD-1 inhibitors**
- **CD38 is ubiquitously expressed on most cells, unlike SFRP2 which is selectively expressed only on tumor cells.** Specifically targeting SFRP2 to inhibit CD38 has advantages (including likely less safety concerns) over targeting CD38 with a CD38 mAb
  - Targeting SFRP2 with IVT-8086 in combination therapy with PD-1 inhibitors should be a good additional therapeutic strategy (in addition to monotherapy) to improve the efficacy to PD-1 inhibitors

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

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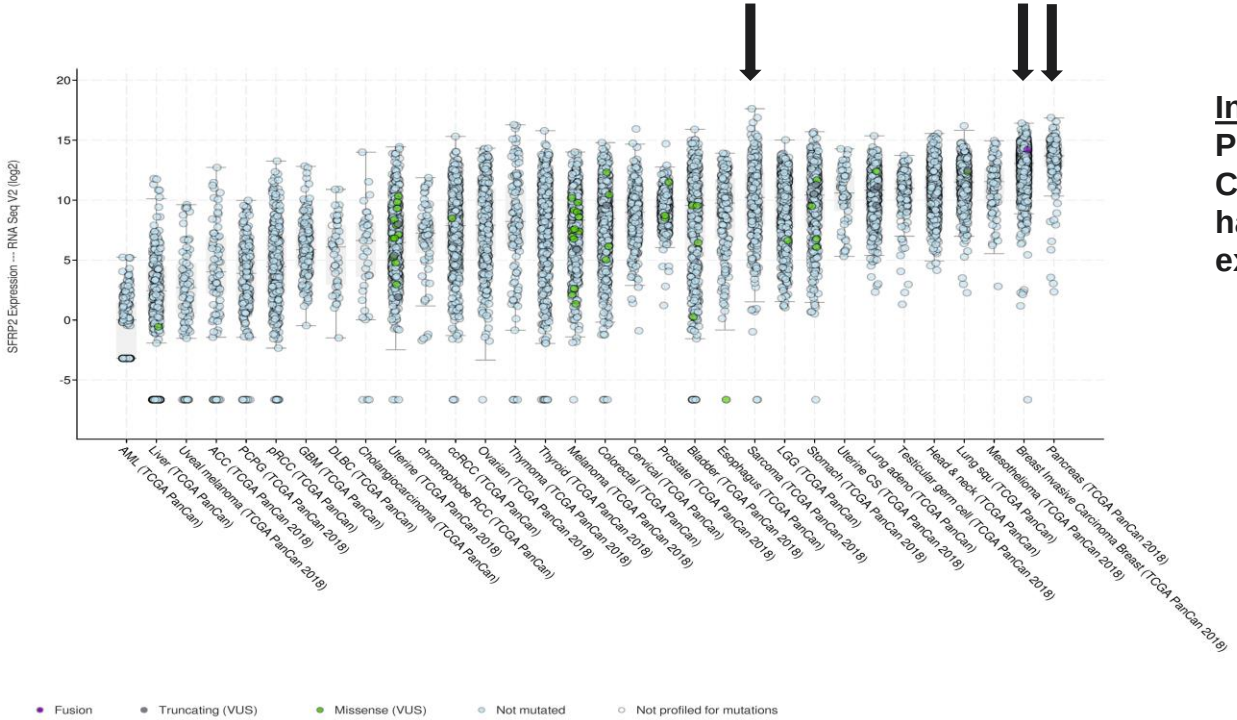
SFRP2 is Overexpressed Across Many Tumor Types

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 Expression Plays a Direct Role in Many Tumors

Innova plans to initially focus on targeted treatment for these cancers

Tumor type	Effect
Breast	Overexpression of transfected SFRP2 in MCF7 breast cancer cells increased their resistance to apoptotic signals in vitro.
Breast (triple negative)	**SFRP2 mAb inhibits triple negative breast cancer in vivo; increases apoptosis, decreases angiogenesis, decreases NFAT activation.**
Angiosarcoma	**SFRP2 mAb inhibits angiosarcoma in vivo; increases apoptosis, decreases NFAT activation**
Renal cell carcinoma	Transfection of SFRP2 in renal cell carcinoma promotes tumor growth in vivo
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 soft part sarcoma	SFRP2 gene expression was found to be elevated in alveolar soft part sarcoma.
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.
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
Melanoma	SFRP2 in aged microenvironment drives melanoma angiogenesis, metastasis and therapy resistance.

Clinical Development Plan for IVT-8086 Initially Focused on Three Cancers, Sarcoma (including Osteosarcoma), Triple Negative Breast, and Pancreatic Cancer

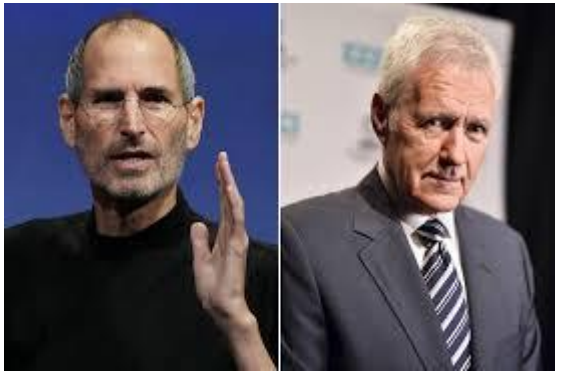
Osteosarcoma (OS) and Other Sarcomas

- 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)

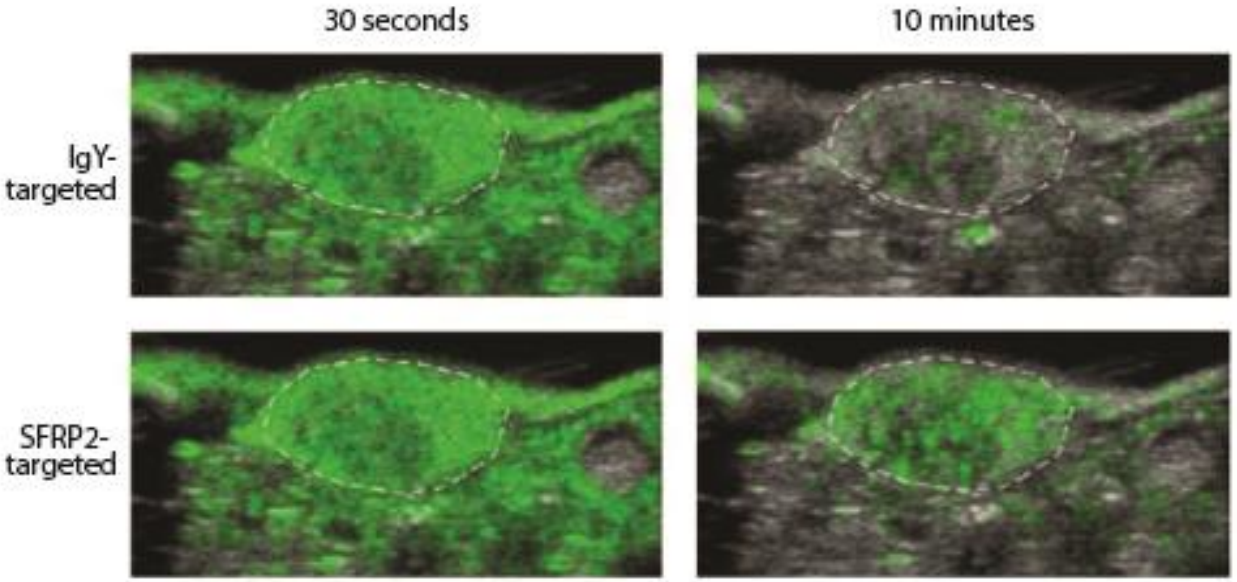
- SFRP2 highly expressed in all human breast cancer subtypes, including TNBC
- In vivo inhibition in tumor growth in chemo-resistant triple negative breast cancer in nude mice
- SFRP2 levels in serum levels in patients across all types of breast cancer was shown to be an independent prognostic factor 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
- 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.

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.

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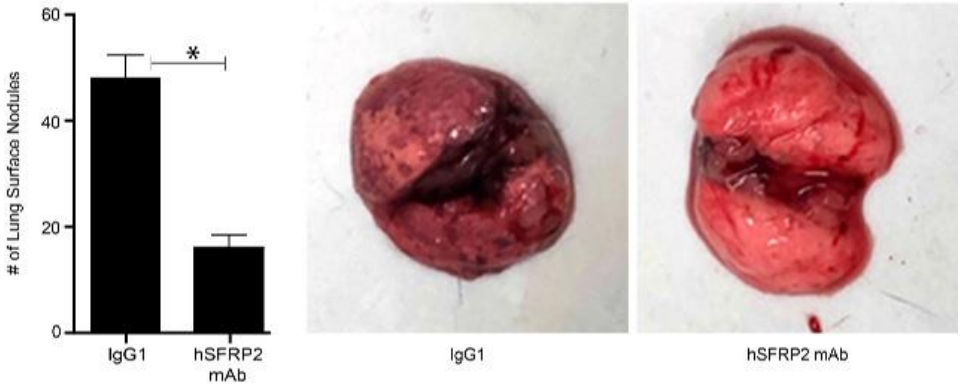
IVT-8086 Monotherapy, in Addition to Combination Studies with a PD-1 Inhibitor Reduced Established Lung Metastases in Osteosarcoma Genetically Engineered Mouse Model (GEMM) Models

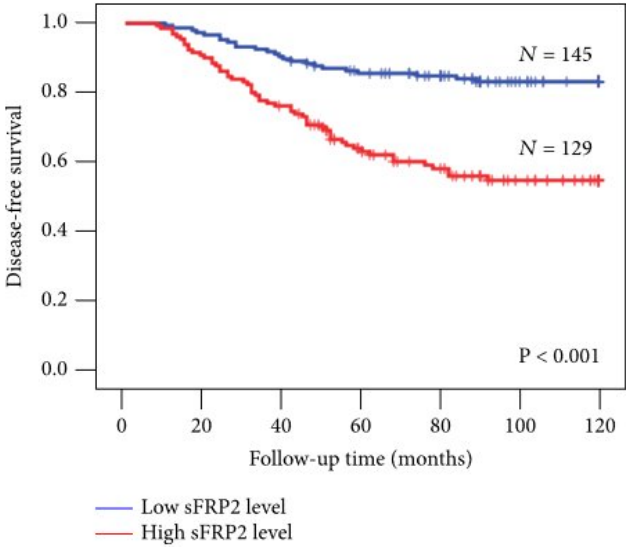


Representative Lungs from Control Mice and Mice Treated with IVT-8086

- **IVT-8086 monotherapy treatment significantly reduced lung surface metastases ($p \leq 0.0001$)**
- **IVT-8086 in combination with a PD-1 mAb was synergistic at inhibiting lung metastases in multiple osteosarcoma GEMM Models ($p < 0.005$)**

Multiple Studies Demonstrate Clinical Validation of SFRP2 as a Therapeutic Target in Cancer Patients - Overexpression Correlates with Poor Patient Outcome

Kaplan-Meier Survival Curve of Breast Cancer Patients



Progression-free survival rate of breast cancer patients with high and low serum SFRP2 levels. SFRP2 plasma levels positively associated with progression-free survival, tumor size, lymph node metastases, TNM stage, and Ki67 rate.

Chumei Huang, Zhuangjian Ye, Jianxin Wan, et al. Disease Markers, vol. 2019, Article ID 6149381, 7 pages, 2019.

SFRP2 Expression in OS Patients and Mouse Model

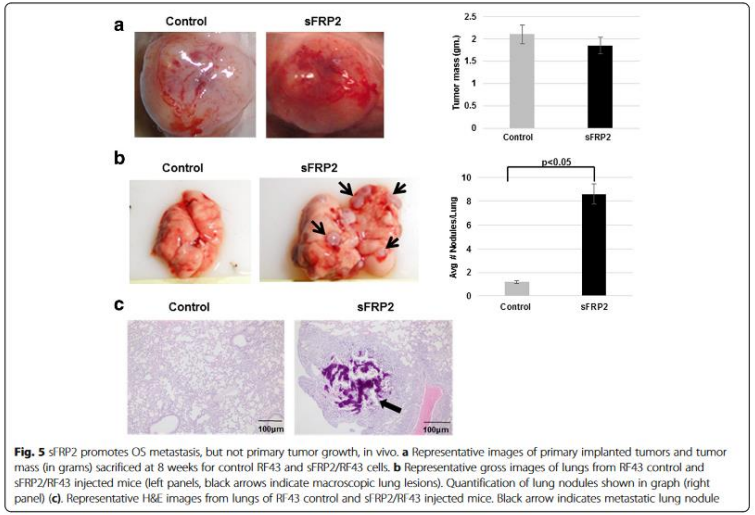


Fig. 5 sFRP2 promotes OS metastasis, but not primary tumor growth, in vivo. **a** Representative images of primary implanted tumors and tumor mass (in grams) sacrificed at 8 weeks for control RF43 and sFRP2/RF43 cells. **b** Representative gross images of lungs from RF43 control and sFRP2/RF43 injected 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

SFRP2 within localized mouse OS cells significantly increased cell migration and invasive ability and enhanced metastatic potential *in vivo*
Strong SFRP2 expression in OS patient samples correlates with poor survival

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

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

Sarcomas (including OS)

Sarcoma is a term used to describe a family of cancers that arise in the body's connective tissues, which include fat, muscle, blood vessels, deep skin tissues, nerves, bones, and cartilage.

Sarcoma is broken down into two types: soft tissue tumors and bone tumors. There are approximately 7000 new cases of soft tissue sarcomas a year in the United States, and approximately 2500 new cases a year of bone cancers.

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 approved since 1991.**

Osteosarcoma is an orphan disease and has an accelerated development pathway and would qualify for a rare pediatric voucher (value $100-300M). The market projection alone for OS is projected as $800M/yr by 2025.

Pancreatic Cancer

Pancreatic cancer is one of the most dangerous malignancies and is the fourth leading cause of cancer-related death in Europe and the United States. Furthermore, pancreatic cancer is expected to be the second most common cause of death in the U.S., 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.**

The Global Pancreatic Cancer market accounted for $1,904.20 million in 2017 and **is expected to reach $4,728.19 million by 2026.**
Source: The "Pancreatic Cancer - Global Market Outlook (2017-2026)" report

Triple Negative Breast Cancer (TNBC)

Breast cancer is the second most common cancer among women in the United States. Research estimates that in 2018 there were 8.6 million five-year prevalent cases of breast cancer worldwide, which by 2027 are expected to increase to 9.3 million cases.

TNBC is one of the most aggressive breast cancers, and accounts for about 15-20 percent of all breast cancers.

The TNBC market will experience rapid growth over the next 10 years across the US, Japan, and five major European markets (France, Germany, Italy, Spain, and the UK).

Global Cancer Monoclonal Antibodies Market & Clinical Trial Insight 2024*

Global Cancer Monoclonal Antibodies Market Opportunity: US$140 Billion

Immuno-Oncology Market, By Type [mAb (Naked, Conjugate), Cancer Vaccines, Immune Checkpoint Inhibitors (PD-1, PD-L1, CTLA-4)], By Application (Lung, Melanoma, Leukemia, Lymphoma) - Global Forecast to 2022*

The Global Immuno-Oncology Market is Anticipated to Cross US$100 Billion by 2022

**Source: Research and Market Reports*

BCC Research report titled 'Checkpoint Inhibitors: Global Markets'

*It states that "according to an analysis by BCC Research, the global market for checkpoint inhibitors is currently worth $14.9 billion. It is forecast to expand at a compound annual growth rate (CAGR) of 14.4% to reach $29.3 billion in 2023.***

** Source: https://drug-dev.com/checkpoint-inhibitors-novel-targets-global-markets/*

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$25M Series A Financing for Development of IVT-8086 (hSFRP2 mAb) as Monotherapy and in Combination with PD-1 Inhibitor – 2.5-3 Year Development Timeline

9 months

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

4 months

20 - 24 months

Initiate and complete Phase 1/2 study in sarcomas including pediatric osteosarcoma (POS) – **designed to support accelerated approval in POS and receipt of voucher**

* Initiate and complete Phase 2 Studies (Monotherapy) patients with triple negative breast (TNB) 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 1 Study, in combination with PD-1 inhibitor in patients with sarcoma, breast and pancreatic cancer

Will be able to obtain early tumor response in patients to IVT-8086 treatment due to frequent CT scans

$7M Funding to Date has been Non-Dilutive

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

- Unique multi-faceted mechanism of action specific to targeting cancer:
  - 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

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

- IVT-8086 monotherapy treatment has demonstrated efficacy (with no adverse safety effects) in multiple animal models implanted with human and mouse GEMM xenografts
  - Combination therapy with IVT-8086 and PD-1 mAb demonstrated synergistic efficacy

- SFRP2 has been validated as an important molecular target in human cancers that has been shown to correlate with patient outcome

- Clearly defined regulatory path
  - Broad therapeutic opportunities across multiple solid tumors including **fast regulatory approval timeline for 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)**

- Composition of matter patents issued, in addition to filed new composition of matter and PCT combination patents