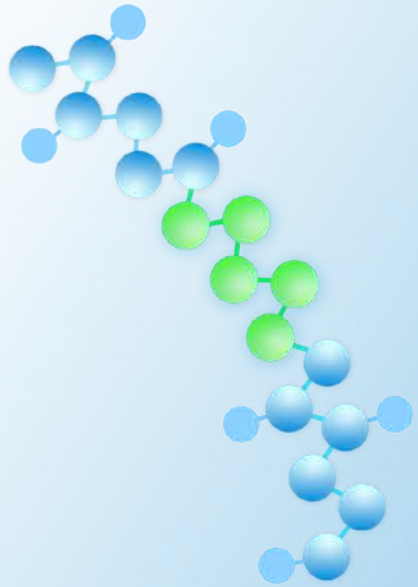
SERPIN PHARMA

Enhancing cell resilience:

A revolutionary approach for inflammatory diseases



November 2022

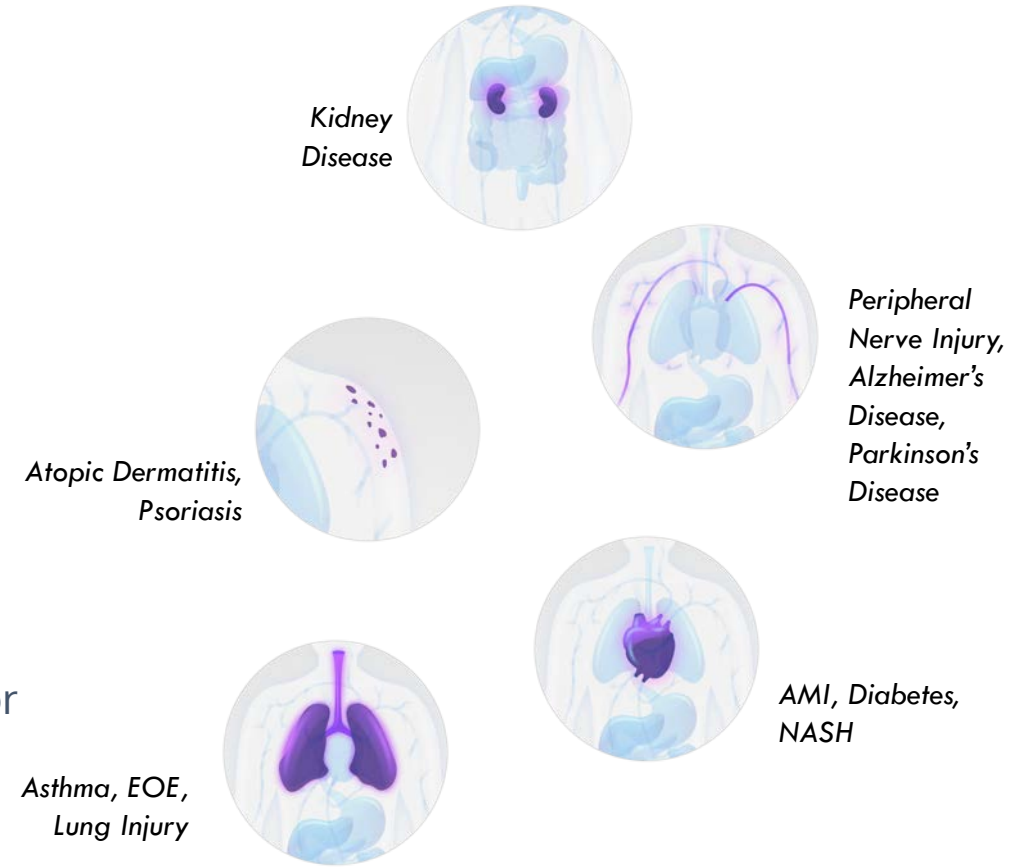
The Problem: Inflammatory Disease is a Growing Epidemic

Inflammation is a natural response to infection or injury and is necessary in order to heal damaged tissues

However: Prolonged or dysregulated immune responses can lead to chronic inflammation and a **variety of diseases**

The *prevalence* of leading inflammatory diseases is growing and continues on an upward trend[1]:

- Inflammatory diseases account for **50% of all deaths**
- **Heart Disease** (30.3 million) – 1 of every 3 deaths (US)
- **Asthma**: 25 million Americans



Treating inflammation with leading anti-inflammatory drugs (i.e. NSAIDs) or immunosuppressive drugs (i.e. steroids) is associated with harmful side effects.

There is an **unprecedented** need to develop a **safe and effective** anti-inflammatory drug to address the overwhelming rise in the prevalence of inflammatory disease.

Source: Wu, Shin-Yi et. Al 2000. Projection of Chronic Illness Prevalence and Cost Inflation. RAND Corporation.

SP16: A Revolutionary Approach to Inflammatory Diseases

- **An anti-inflammatory drug platform**
  - Our **first-in-class** peptide therapeutics **resolve inflammation** by re-instating immune regulation (homeostasis) (not immunosuppressive)
    - Derived from Alpha-1 Antitrypsin (A1AT), a SERPIN protein with an excellent safety profile; been used in the clinic for 30+ years
      - A1AT is being explored for orphan diseases but has developmental challenges
      - **SP16 is a small excerpt (5%) with higher potency (300x)**
  - **SP16's unique mechanism of action is very well defined:**
  - **Safe**: Completed Phase 1 and Phase 2A clinical trials (AMI) with no adverse effects
  - **Versatile**: Mitigates inflammation and balances immune response in a variety of diseases; **Topical, injectable, or oral** delivery
  - **Large market potential**

Targeted Potent Balancing

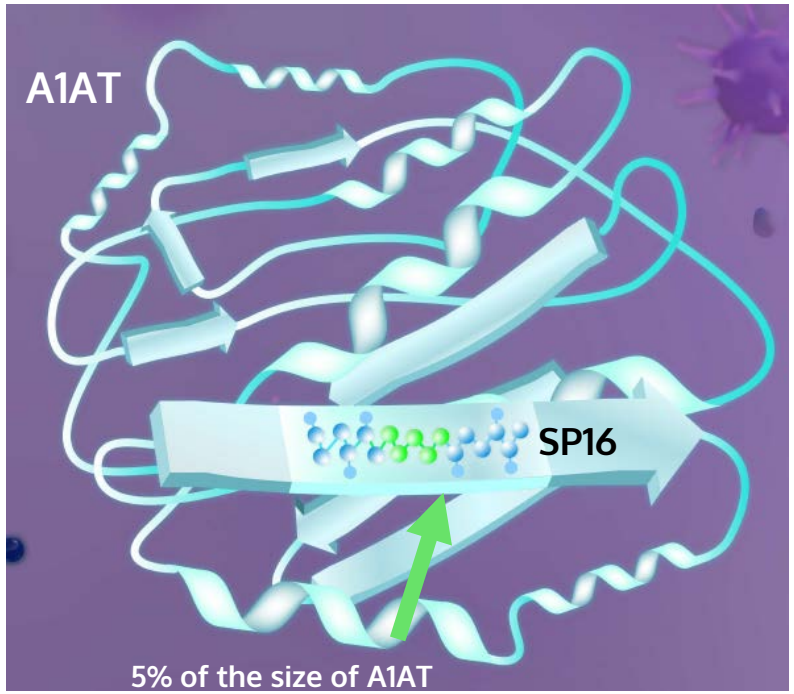
By selectively isolating a **key portion** of a **natural Serpin** protein, our **targeted** therapeutic, known as SP16, **restores balance** to harmful inflammatory environments, creating an entirely **new class of therapeutics** for unmet medical needs.

SP16's Drug Profile

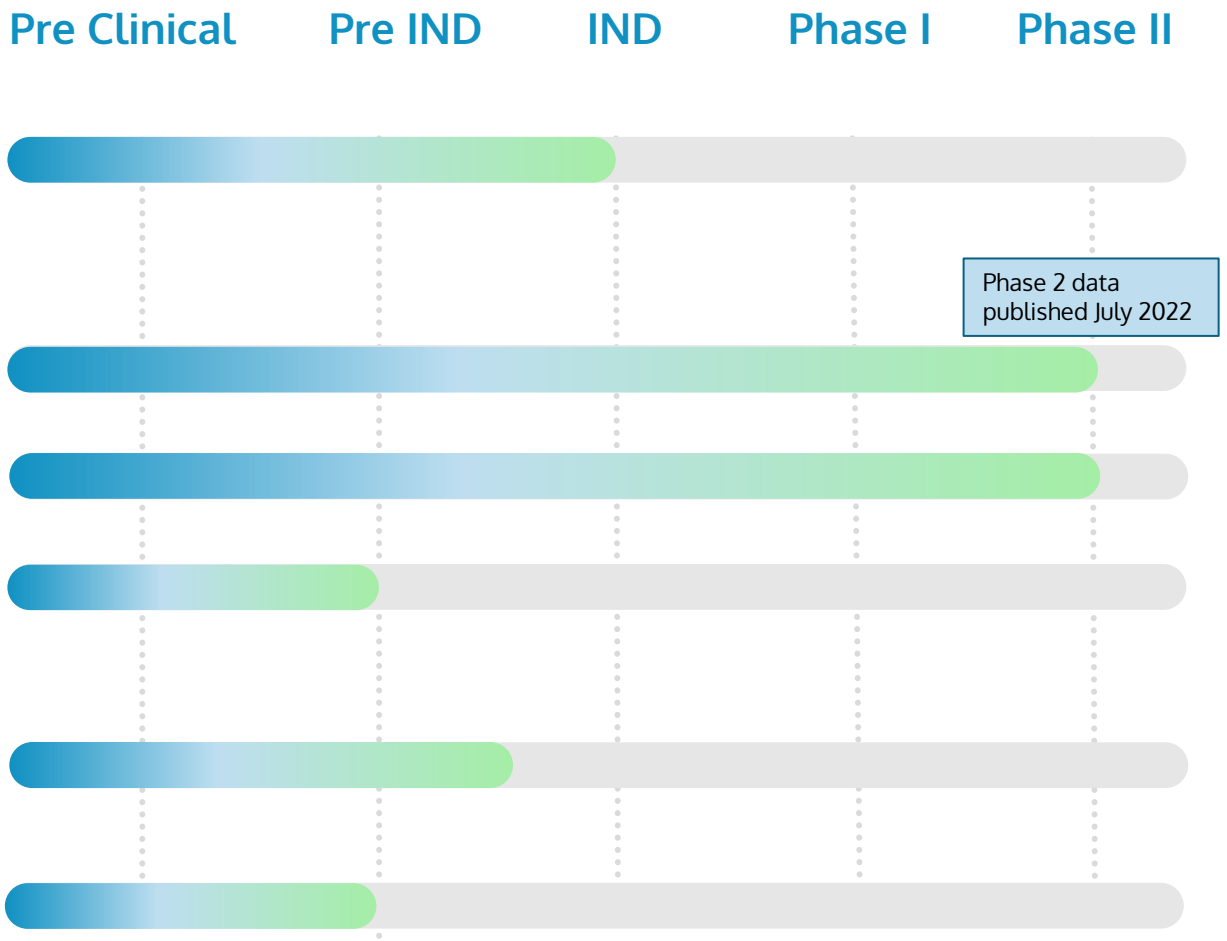
SP16 is a short peptide (17 aa)

- Contains the aa encoding for anti-inflammatory functions; proinflammatory sequences are removed from c-terminus fragment
  - Modifications made to one aa in the core motif
- High binding affinity to LRP1
- Highly selective
- **No off-target effects observed (134 receptors)**
- Soluble water-based formulation (pH 5.8-6.2)
- $T_{1/2}$ is ~ 3.8 hrs with PD effect ~>7 days
- **Pulsatile, second messaging thru LRP1**
  - expression on immune cells, epithelial cells, endothelial cells, brain, lung, heart
  - **increased further during inflammation**
- Stability shows no change after 24 mo. at 4°C

SP16 is a 17aa peptide derived from the c-terminus of A1AT



Pipeline



Orphan

Eosinophilic Esophagitis (EoE) (Oral)

Pre IND meeting Completed

Acute

Acute Myocardial Infarction (AMI) (Injectable)

Acute Lung Injury[1] (Injectable)

Awarded $1.25M Collaboration with Dr. Shim, UVA Medical Center

Acute Kidney Injury (Injectable)

Chronic

Inflammatory Skin Diseases (Topical)
(Atopic Dermatitis, Alopecia Areata, Pemphigus Vulgaris)

Chemotherapy-Induced Peripheral Neuropathy (CIPN) (Injectable)

Awarded $400K from National Cancer Institute

The Science of Serpin

- **Mechanism of Action of SP16 Drug**
- **Short size, cyclic, SP16 analogs for oral delivery**
- **SP16 Data in pain and peripheral neuropathy**
  - Chemotherapy-Induced Peripheral Neuropathy
- **SP16 Data available upon request:**
  - Acute Myocardial Infarction
  - Acute Kidney Injury
  - Eosinophilic Esophagitis (EoE)
  - Inflammatory Skin Diseases/Atopic Dermatitis
  - Lung Injury

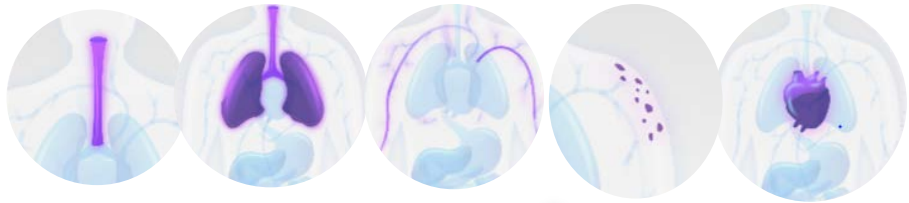
SP16 is a Potent LRP1 Agonist

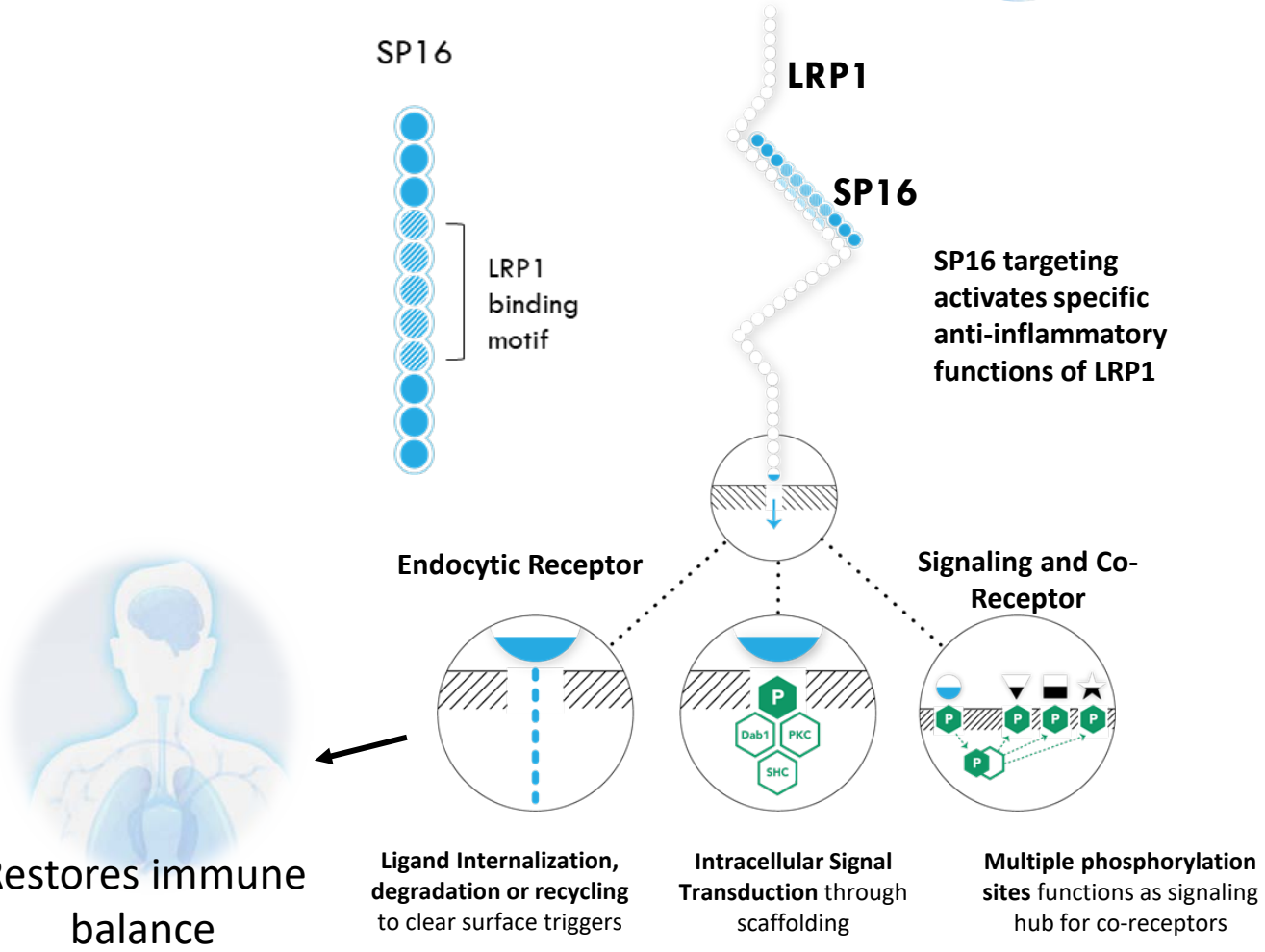
Mechanism of Action

SP16 targets *Low density lipoprotein receptor-related protein 1* (**LRP1**), an **endocytic** and **signaling** receptor that mediates cellular responses that drive inflammation

- Balances innate immune responses (inflammasome, cytokine output) – not immune suppressive
- Strong promotor of **autophagy** activity: Removes harmful surface debris and promotes healing
- Protects cells from inflammatory injury and aids in tissue repair

Imbalanced immune responses contribute to inflammatory diseases



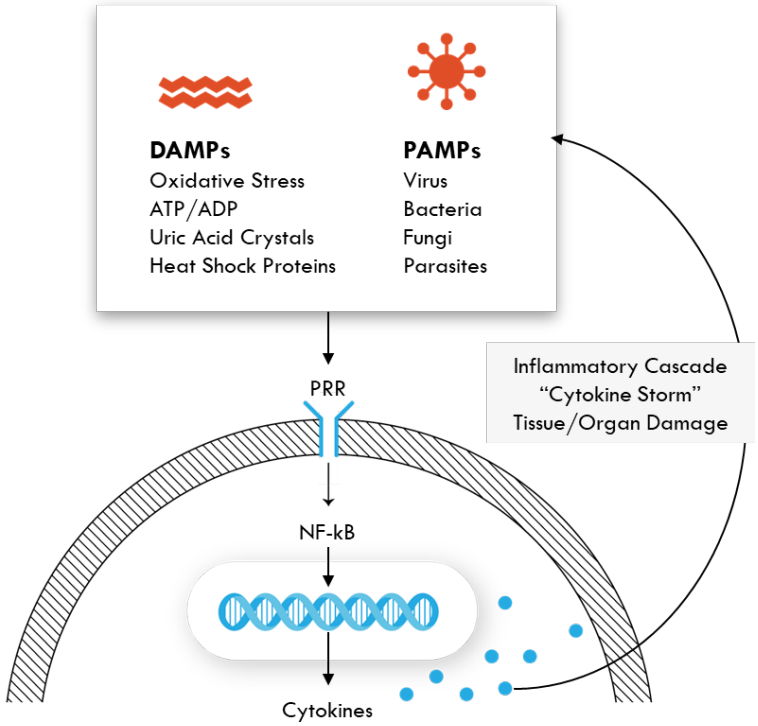


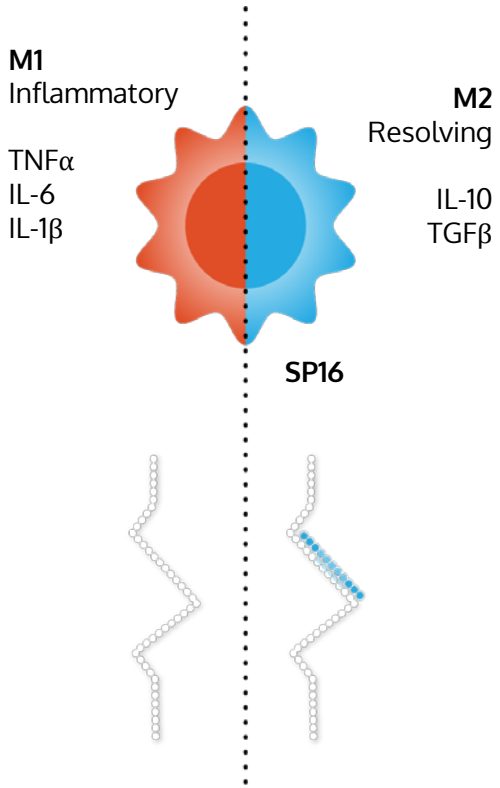
Anti-inflammatory Effects of LRP1 Agonists

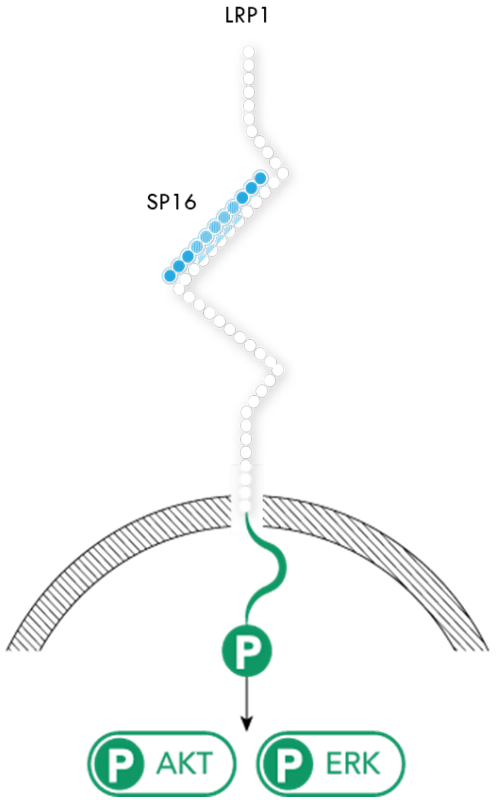
Balance Innate Immune Responses:
- Shuts down pro-inflammatory NF-kB
- Removes surface triggers PAMP/DAMPs

Promote Anti-Inflammatory Profile
- Decreases TNFa, IL-6 (pro-inflammatory)
- Increases IL-10, TGFβ (anti-inflammatory)

Preserve Tissues Repair Pathways
- Activates Akt/ERK/mTOR specific signaling pathways







Demonstrated Safety and Efficacy for SP16

Pre-clinical Safety

- Non-immunogenic peptide
- SP16 is a short, linear peptide with high homology to endogenous AAT and is therefore expected to be non immunogenic
- No peptide-specific antibodies were found in sera of mice treated up to 6 months
- Attempts to generate monoclonal antibodies directed against SP16 in the presence of strong adjuvants were unsuccessful
- Receptor binding studies clear

Clinical Safety

Phase I Safety Trial

- Double blind, placebo controlled, ascending dose escalation study, single subcutaneous injection monitored continuously for 12 hours and followed for up to 7 days
- No Serious Adverse Events at Highest Dose (0.2mg/kg)
- All test results were unchanged
- ECG, CBC, liver enzymes, cv biomarkers, coagulation, inflammatory biomarkers

*Wohlford, George F et al. "A phase 1 clinical trial of SP16, a first-in-class anti-inflammatory LRP1 agonist, in healthy volunteers." PloS one vol. 16,5 e0247357. 6 May. 2021, doi:10.1371/journal.pone.0247357

Phase II Clinical Trial (AMI pilot study)

- Subcutaneous administration of 0.2 mg/kg SP16 was safe and well tolerated in STEMI patients (n=10)
- Trial completed December 2021; results expected to be published 2Q/3Q 2022

Phase IB clinical study in COVID-19 hospitalized patients

- Currently enrolling patients; study expected to be completed 4Q 2022/1Q 2023

Significant Proof of Concept

Through collaborations with experts in their disease fields, we have obtained a large body of evidence showing the anti-inflammatory and protective effects of SP16 in many different indications:

- AMI
- Eosinophilic Esophagitis (Allergic Inflammation)
- Peripheral Nerve Injury/Pain
- Lung Injury (ARDS/COVID-19)
- Kidney Injury
- Skin inflammatory diseases (AD, Acne)
- Rheumatoid arthritis
- Gout
- GVHD

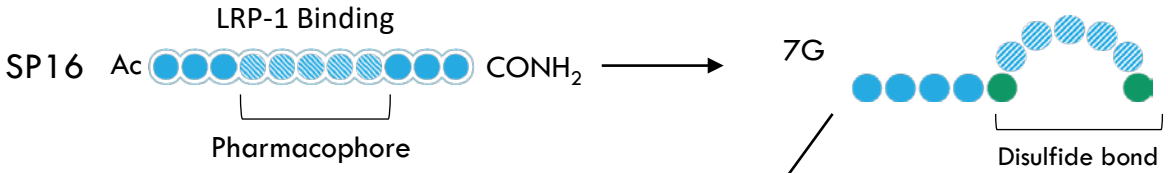
Second Generation Analogs

We have designed next-generation analogs modeled off of the **SERPIN-LRP-1** interaction

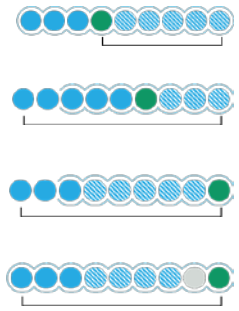
Like SP16, these peptide analogs are designed as LRP-1 agonists

- In-vitro data shows increased anti-inflammatory efficacy (TNFa, NFKb, IL6)
- In-vivo data in several models shows PD effects
- Improvement in PK properties vs. SP16
- **Oral availability** of lead analog (A2.5) is 7%
- Novel IP (patent application filed in 2022)

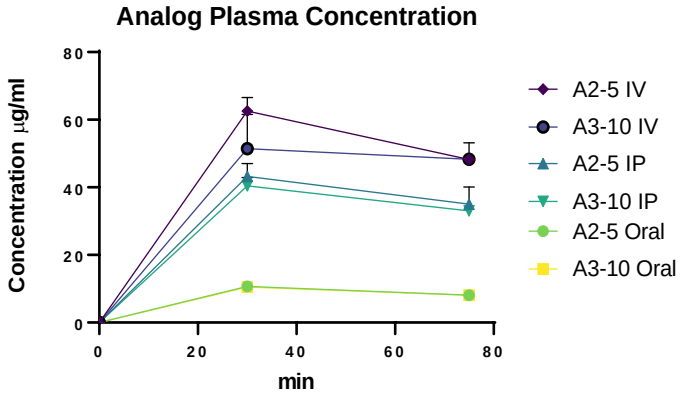
Proof of concept Analog



2nd Generation Analogs



Analog	NFκB IC50 (µg/ml)	TNFα IC50 (µg/ml)
A2-1	7.85	13.60
A2-2	5.17	8.85
A2-3	3.45	8.23
A2-4	7.41	13.90
A2-5	2.54	7.12
A2-6	9.54	32.79
A2-7	7.55	30.00
A2-8	30.57	16.23
A2-9	20.18	18.71
7G	NA	65.90
SP16	52.11	57.37
A1-15	NA	33.26



Strong Intellectual Property Protection

Exclusivity

2041	SP16: 12 issued Patents
2046	Analogs

Thirteen patent applications (3 families); 12 issued patents; IP covers Composition of Matter as well as the Use of Serpin peptide drug and analogs

SP16 is a fragment of a natural molecule with a modification to the sequence that yielded an enhanced affinity to the LRP1 receptor (expiration 2041)

SP16 analogs are shorter peptide drugs molded on SP16 with extensive modifications outside of the binding motif (expiration of patent 2046)

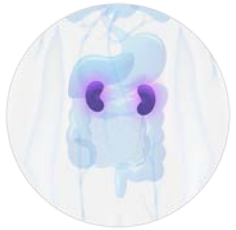
Cross-validation of Platform Technology by Key Opinion Leaders

Eosinophilic Esophagitis (EoE)

- **Marc Rothenberg, MD, PhD,** Cincinnati Children's Hospital Center for Eosinophilic Disorders
- **Nurit Azouz, PhD,** Cincinnati Children's Hospital Medical Center

Inflammatory Skin Diseases

- **Seth Orlow, MD, PhD,** NYU Langone Hospital, NYC Health and Hospital-Bellevue
- **Emma Guttman-Yassky, MD,** Mount Sinai

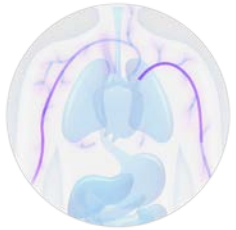


Acute Kidney Injury (AKI)

- **Tilman Jobst-Schwan, MD,** Friedrich-Alexander-Universität Erlangen-Nürnberg
- **Mario Schiffer, MD,** Friedrich-Alexander-Universität Erlangen-Nürnberg
- **Shuta Ishibe, MD,** Yale New Haven Hospital

Acute Myocardial Infarction (AMI)

- **Antonio Abbate, MD, PhD.** University of Virginia



Pain & Neuromuscular Disorders

- **Wendy Campana, PhD,** University of California San Diego
- **Imad Damaj, MS,** Virginia Commonwealth University
- **Gordon Smith, MD, FAAN**, Virginia Commonwealth University
- **Michael Gitcho, PhD,** Delaware State University

Lung Injury & Infectious Diseases

- **Y.Michael Shim, MD,** University of Virginia
- **Nazira El-Hage, PhD,** Florida International University
- **Kylene Kehn-Hall, PhD**, Virginia Tech

Additional Key Opinion Leaders:

- **Christopher Dearth, PhD,** DoD-Extremity Trauma & Amputation Center of Excellence
- **Stephen Goldman, PhD,** DoD-Extremity Trauma & Amputation Center of Excellence
- **Masoud Manjili,** DVM, PhD, Virginia Commonwealth University
- **Mark Prausnitz,** PhD, Georgia Tech
- **Emanuel Petricoin,** PhD, George Mason University; Ceres Nanosciences

SP16: A platform technology with proven effects in a wide range of inflammatory diseases

Our therapeutic restores immune balance by targeting a receptor that plays a key role in mitigating inflammation

Atopic Dermatitis (AD) (eczema) is an inflammatory skin disease that can remain uncontrolled with standard care options

In preclinical models, SP16 was shown to:

- Significantly improve disease outcomes (dryness, redness, itching)
- Inhibit the specific immune responses that activate the inflammatory cascade in the skin (TH2 mediators and TSLP)
- Significantly reduce eosinophil infiltration in the skin
- Provide a convenient topical delivery option

Eosinophilic Esophagitis (EoE) is an allergic inflammatory disease and an orphan indication with limited treatment options

In preclinical models, SP16 was shown to:

- Control clinically significant drivers of allergic inflammation, including TSLP and TH2 associated cytokines
- Significantly reduce eosinophil infiltration at the site of injury
- Mediate clinically validated cell signaling pathways (JAK/STAT)
- Provide a convenient delivery method

Acute Kidney Injury (AKI) is defined as loss of kidney function and is a large risk factor of heart surgery. Cardiac-surgery-associated AKI is further associated with other adverse outcomes, including chronic kidney disease (CKD) and death.

In preclinical models, SP16 was shown to:

- Protect kidney cells from hypoxic induced damage
- Reduce inflammatory mediated cellular responses in kidney cells
- Improve kidney damage in a doxycycline-inducible mouse model of proteinuric kidney disease

SP16: A platform technology with proven effects in a wide range of inflammatory diseases

Our therapeutic restores immune balance by targeting a receptor that plays a key role in mitigating inflammation

Acute Lung Injury (ALI) and acute respiratory distress syndrome (ARDS) are life-threatening respiratory disorders associated with an uncontrolled inflammatory response. Severe respiratory inflammation is a critical hallmark of COVID-19 infection.

In preclinical models, SP16 was shown to:

- Increase survival and reduce cytokine levels (comparable to the corticosteroid dexamethasone)
- Have bioavailability in the lung following parenteral administration
- Reduce key mediators needed for viral entry and spread
- Have broad-spectrum of anti-viral effects (including SARS-CoV-2, the virus that causes COVID-19, and other emerging infectious diseases)

Chemotherapy-induced peripheral neuropathy (CIPN) is the result of damage to the peripheral nerves and is associated with weakness, numbness, and pain. CIPN is one of the most frequently experienced adverse effects of patients receiving cancer treatments. Because of this, effective doses of chemotherapeutic agents are reduced or treatment is discontinued

In preclinical models of neuropathy, SP16 was shown to:

- Alleviate neuropathic pain
- Reduce inflammation at the site of nerve injury
- Improve nerve survival, growth, and regenerative signaling

Acute myocardial infarction (AMI) is associated with an intense inflammatory response that can increase the risk of Heart Failure

In Preliminary Phase 2a clinical trial, SP16 treatment was associated with the following trends:

- Reduce biomarkers of infarct size
- Reduce overall inflammation
- Improve long-term heart function (one-year post-treatment)

Manuscripts Covering Serpin's Technology

- Low-Density Lipoprotein Receptor–Related Protein-1 Is a Therapeutic Target in Acute Myocardial Infarction – ScienceDirect (https://www.sciencedirect.com/science/article/pii/S2452302X17302024) 2017
- Frontiers | Low Density Lipoprotein Receptor-Related Protein-1 in Cardiac Inflammation and Infarct Healing | Cardiovascular Medicine (frontiersin.org) (https://www.frontiersin.org/articles/10.3389/fcvm.2019.00051/full) April 16, 2019
- A phase 1 clinical trial of SP16, a first-in-class anti-inflammatory LRP1 agonist, in healthy volunteers (plos.org) (https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0247357) May 6, 2021
- α1 - Antitrypsin derived SP16 peptide demonstrates efficacy in rodent models of acute and neuropathic pain (wiley.com) (https://faseb.onlinelibrary.wiley.com/doi/epdf/10.1096/fj.202101031RR) November 23, 2021
- Safety, tolerability and effects of a single subcutaneous ad... : Journal of Cardiovascular Pharmacology (lww.com) (https://journals.lww.com/cardiovascularpharm/Abstract/9900/Safety,_tolerability_and_effects_of_a_single.79.aspx) July 12, 2022
- Anti-inflammatory therapy for acute coronary syndromes: is i... : Journal of Cardiovascular Pharmacology (lww.com) (https://journals.lww.com/cardiovascularpharm/Citation/9900/Anti_inflammatory_therapy_for_acute_coronary.85.aspx) July 20, 2022

Peripheral Neuropathy and Pain

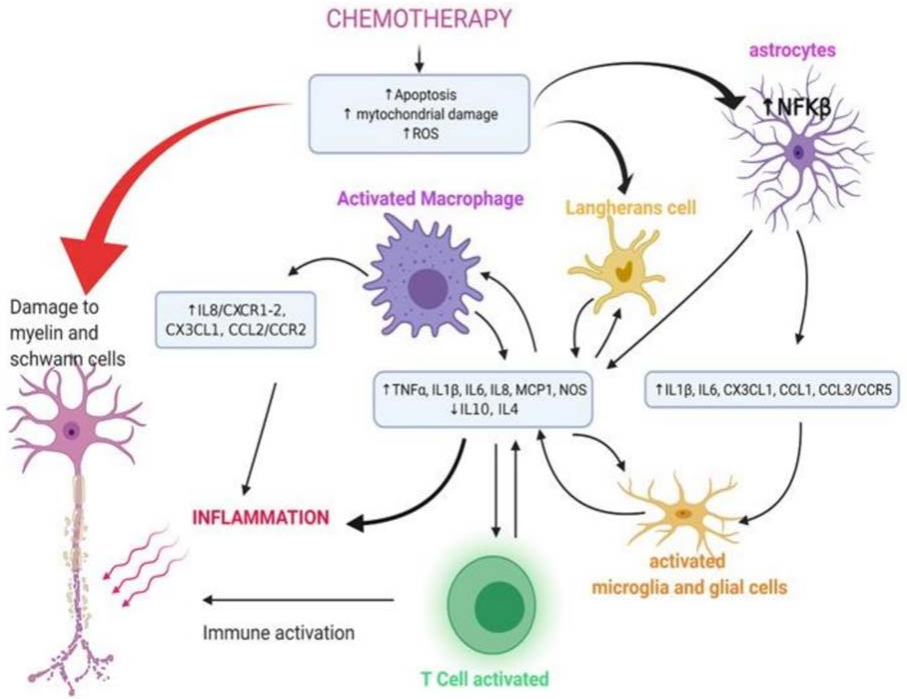
Applications in:

- Chemotherapy-induced Peripheral Neuropathy (CIPN)

In collaboration with Campana Laboratory
Department of Anesthesiology and Program in Neuroscience
University of California, San Diego

Key Mechanisms in Chemotherapy-Induced Peripheral Neuropathy

- Chemotherapy is associated with a myriad of adverse effects, including the induction of peripheral neuropathy (CIPN).
- CIPN dramatically reduces the quality of life for patients while also increasing the risk of treatment discontinuation or poor adherence.
- CIPN results from **systemic and local inflammatory mediators impacting the PNS**, increasing sensitivity (i.e., allodynia), causing pain, and producing other neuropathic symptoms (e.g., numbness, tingling, etc.).



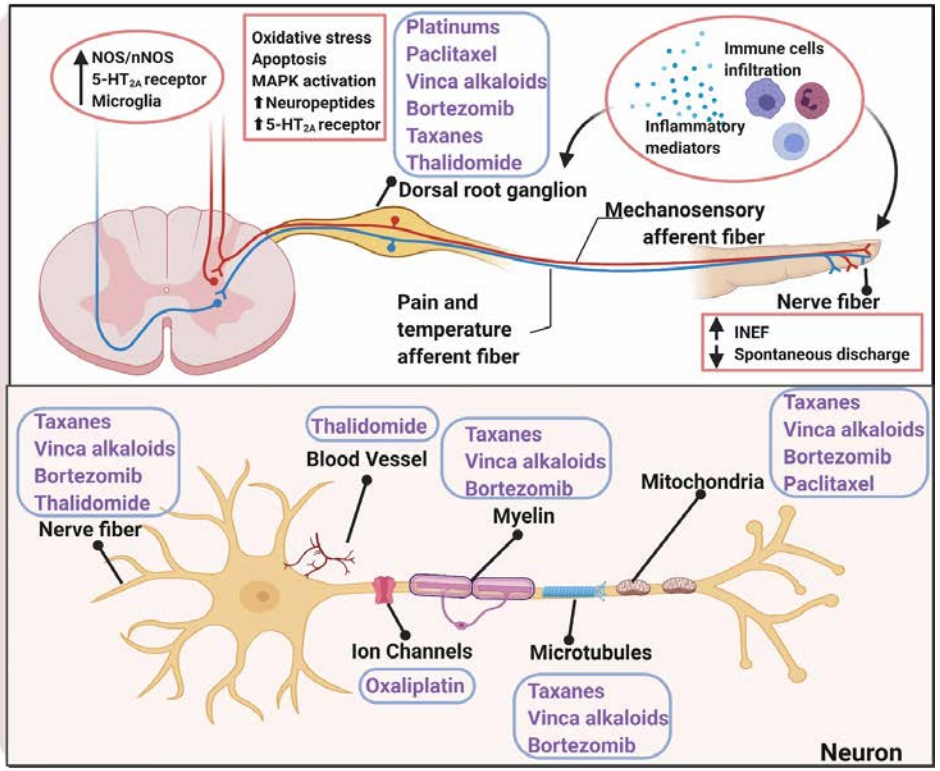
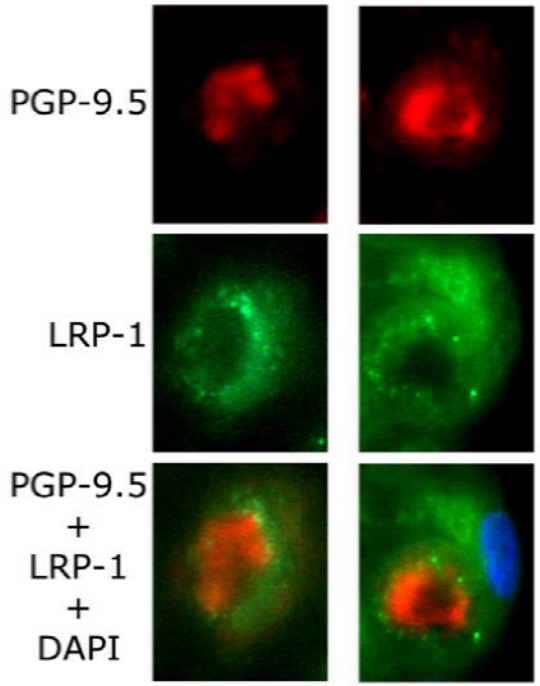


Image: Yang, Y., Zhao, B., Gao, X. et al. J Exp Clin Cancer Res 40, 331 (2021). https://doi.org/10.1186/s13046-021-02141-z

Low-density lipoprotein receptor-related protein-1 (LRP1) in Schwann cells

Expressed in response to nerve injury

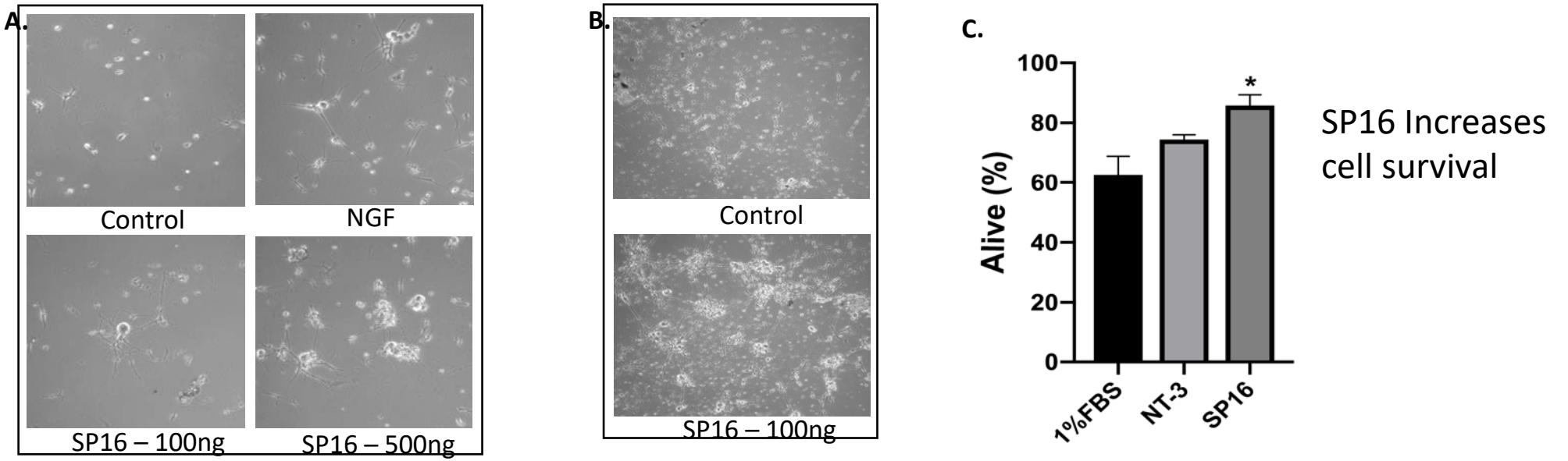


Binds numerous ligands produced in injured PNS including: MMP-9, fibronectin, tPA, α2-macroglobulin

Campana et al., (2006) J Neuroscience

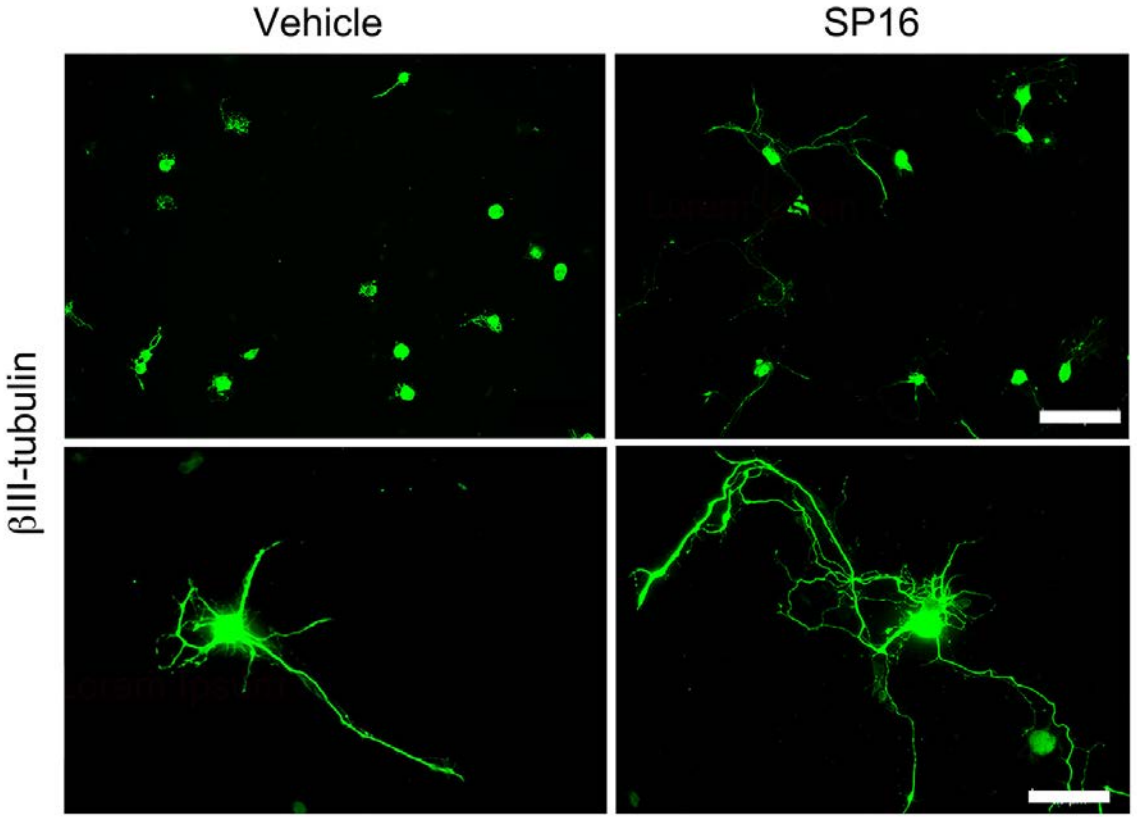
SP16 promotes neurite outgrowth and survivability in adult DRG cultures

- Current therapies for peripheral neuropathies are directed at symptomatic control because no effective regenerative treatment exists
- Dorsal root ganglia (DRG) derived sensory neuron culture system is a useful model in evaluating the pathogenic mechanisms of peripheral neuropathies
- **Here, we show SP16 has regenerative and pro-survival properties in culture model of peripheral neuropathy – Even at low doses and more so than positive control (Nerve Growth Factor (NGF)**

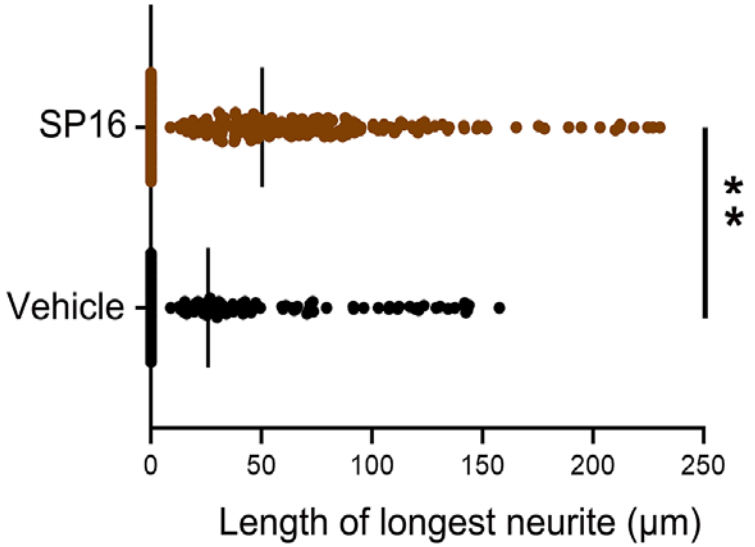


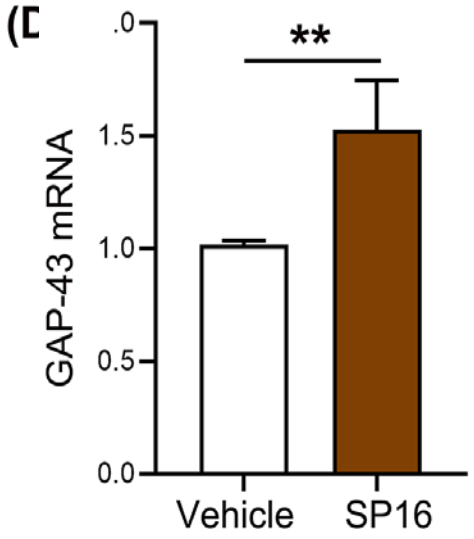
SP16 promotes neurite outgrowth and survivability of adult DRG neurons. *A)* High-power representative phase contrast images of cultured primary adult DRG neurons at 48 hours. DRG cultures are untreated (control), treated with NGF (positive control), or treated with SP16 (100 or 500ng/mL). *B)* Low-power representative phase contrast images of cultured primary adult DRG neurons at 96 hours. DRG cultures are untreated (control), or treated with SP16 (100 ng/mL). *C)* Trypan blue survivability assay at 96 hours, n=1 (*, $p<0.05$).

SP16 promotes neurite length and growth associated protein-43 (GAP-43) in adult primary rat DRG neurons



54 hours in primary culture

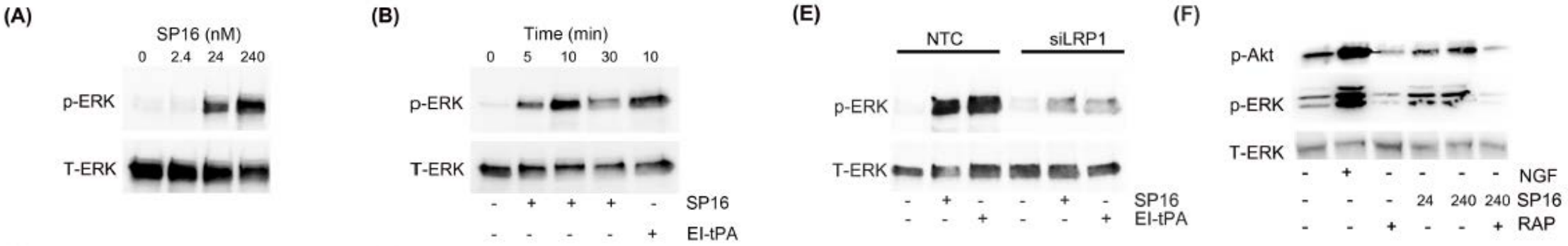




Wang et al., 2021 *FASEB J*

SP16 works through LRP1 to induce pro-survival signaling in nerve cells

We tested SP16 induced cell signaling in PC12 cells, and showed that SP16 dose dependently induced ERK1/2 and Akt activation that was lost when silencing LRP1 (siLRP1) or with blocking by antagonist, RAP (150 nM)



In PC12 cells, SP16 activates transient cell signaling in an LRP1 dependent manner. A, Dose dependent (0-240 nM) activation of phospho-ERK by SP16 after 10 mi n. B, Timecourse (0-30 min) of SP16 (240 nM) activation of phospho-ERK. Last lane (far right) shows activation of phospho-ERK1/2 by a known LRP1 activator, EI-tPA. Equal amounts of protein lysates (20 µg) were loaded per lane. Immunoblot analysis detects phopsho-ERK and total ERK1, as a loading control. E, Representative immunoblot of phospho-ERK activated by SP16 (240 nM) over time 48 hours after transfection with NTC or siLRP1. F, Immunoblot showing activation of phospho-Akt and phospho-ERK with vehicle or SP16 (24 or 240 nM) for 10 mins and in some wells, pretreated with RAP (150 nM) for 15 min. NGF (0.36 nM) for 10 min served as a cell signaling control. Equal amounts of protein lysates (20 µg) were loaded per lane. Total ERK served as a loading control.

SP16 Pain Studies

PURPOSE: to determine whether SP16 administration influences acute and chronic pain phenotypes

IN VIVO MODELS: Intraplantar Formalin (acute, tissue injury), Intraplantar Capsaicin (acute nociception) and Partial nerve ligation (PNL; neuropathic pain)

TREATMENT: Treat with SP16 (50ug/25g mouse) 1 hour prior to Formalin Studies and Capsaicin, and every day for PNL studies (including day of surgery)

ENDPOINTS:

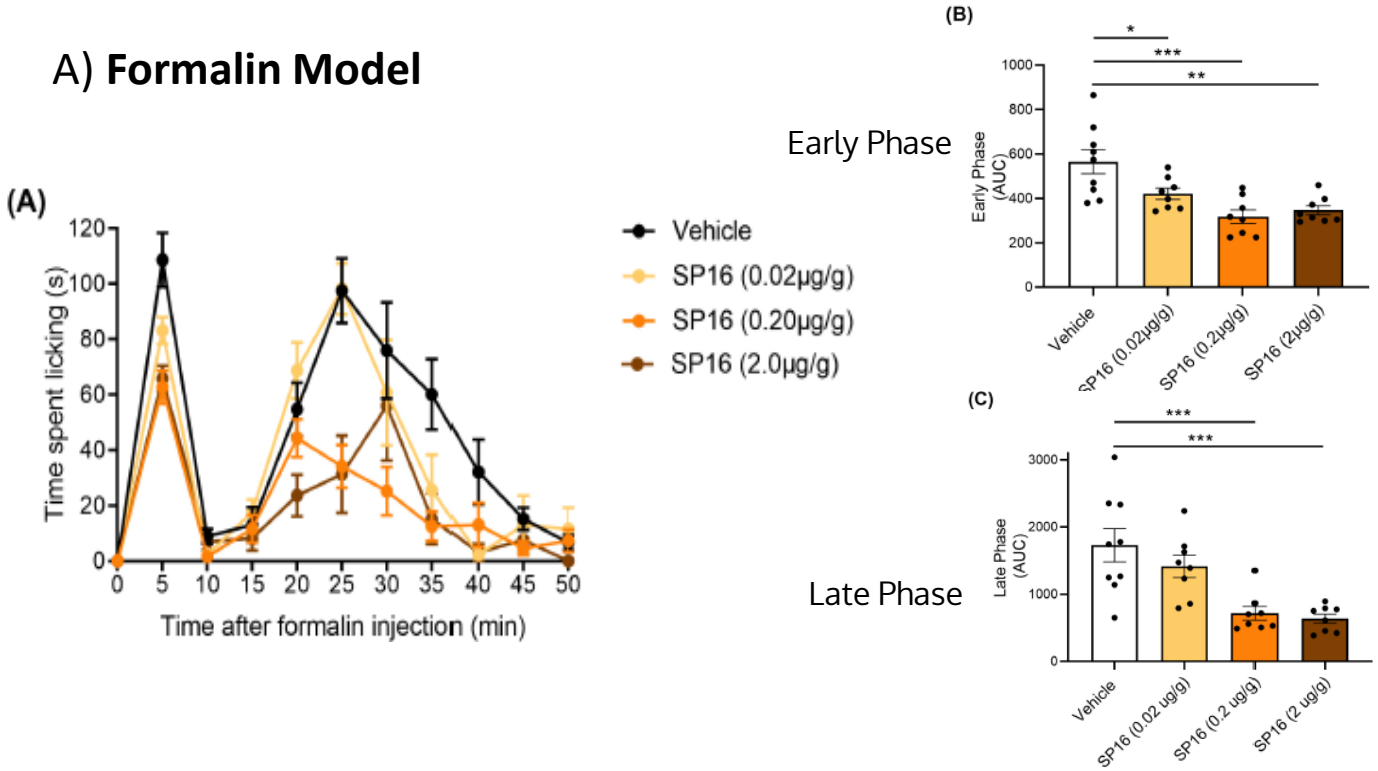
- Formalin and Capsaicin Tests: Ipsilateral foot licking; duration (sec) in 5 minute windows
- PNL: evoked pain measurements (tactile allodynia), sciatic nerve and DRG collection for cellular and molecular analysis (inflammatory cells, markers of innate immunity)

SP16 has Analgesic and Anti-inflammatory Effects in Several Pain Models

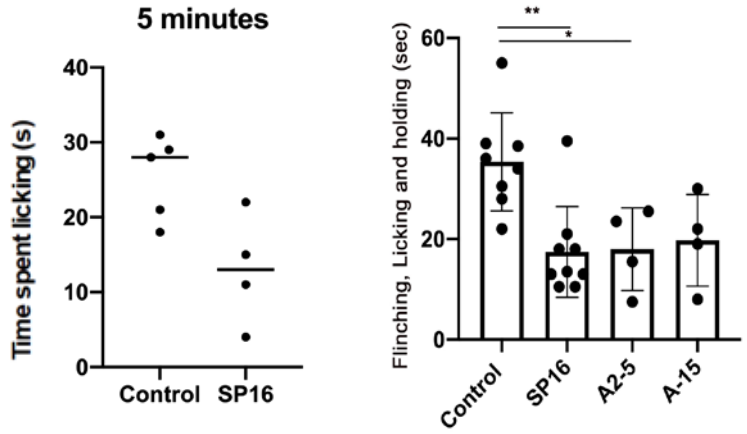
A) **Formalin Test**: a tissue injury model with biphasic nociceptive responses used to assess efficacy in neuropathic pain
SP16 affects both the first acute nociceptive phase (**reduced first peak – Early phase AUC**) and the second inflammatory phase of the formalin test (**delayed second peak- Late phase AUC**);

B) **Capsaicin test**: Acute pain model; short-lasting (minutes) but intense pain associated with hyperalgesia
Reduction of time spent licking (Pain associated behavior) with SP16 treatment and analogs A2-5 and A1-15 (at lower dose)

A) **Formalin Model**



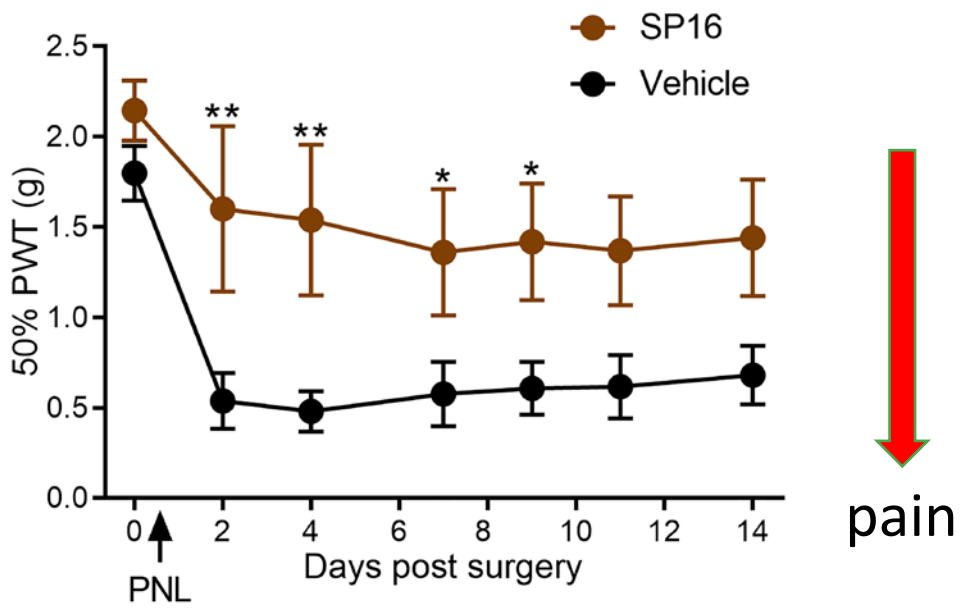
B) **Capsaicin Model**



A) Mice administered SP16 (0.2µg/g, 0.2µg/g or 2.0µg/g), SC, 1hr prior to Formalin (intraplanar 2.5%) and observed for licking behavior for 50 min. SP16 has analgesic effects comparable to low-dose morphine. (*, p<0.05, **, p<0.01). N = 5-6 mice per group. B) Mice administered SP16 as in (A) and then given Capsaicin (25ng, intra-plantar), observation by blinded observer for 10 min. with recorded time spent licking (n=5).

SP16 prevents the development and maintenance of tactile allodynia in mice

SP16 reduces tactile allodynia (evoked pain response)

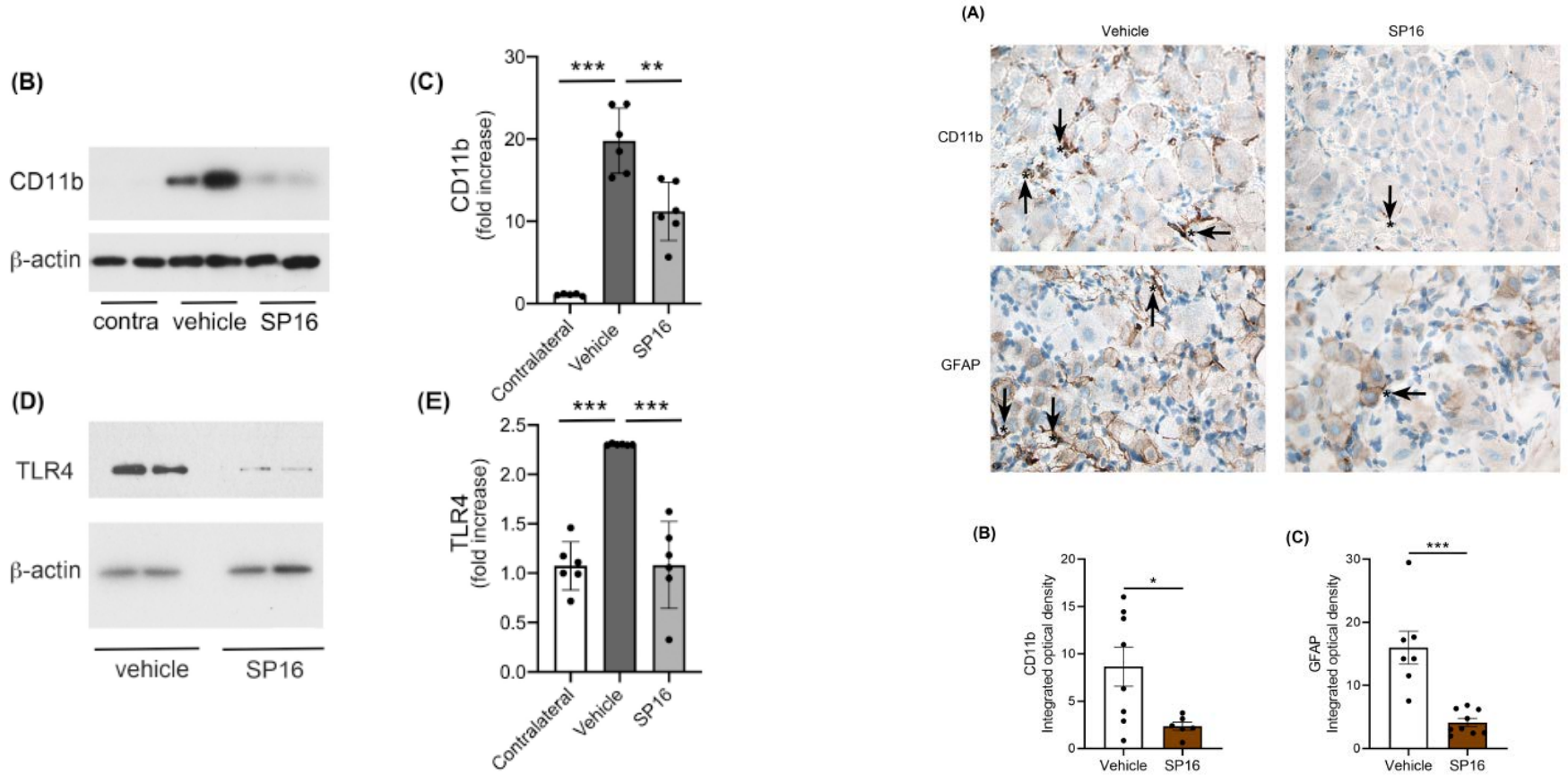


50 ug/day/mouse (25 g)

Partial Nerve Ligation Model: Mice (n=10) given SP16 50µg before partial (1/3) ligation of the sciatic nerve, and daily thereafter, mice observed for evoked pain (hind paw withdrawal response to von Frey filament stimulation).

SP16 Treatment Reduces Inflammatory Infiltration after Nerve Injury

SP16 treatment reduced inflammatory cell infiltration (CD11b) and activation of innate immunity (TLR4) into the nerve in the PNL model



Wang et al., 2021 *FASEB J*

Inflammatory cell recruitment into the DRG after PNL is reduced by SP16 treatment. A, Transverse sections of L4 DRG immunostained for CD11b and GFAP after vehicle or SP16 treatment two days post PNL. CD11b and GFAP immunoreactivity in SP16 treated DRGs are minimal. Nuclei are stain with hematoxylin (blue). ***P<0.05) immunoreactivity in vehicle and SP16 treated injured DRGs.

SP16 does not interfere with chemotherapy treatment

Preclinical study in tumor xenograft model:

Tumor Xenograft Model
BXPC3 (5x10^6)
SC into flank

Tumor size 200 mm^3

Treatments 5 days daily for 1st week then TIW (3x/week) for 2 weeks.

- No treatment (PBS)
- Irinotecan (10mg/kg)
- SP16 (12.5 mg/kg) + Irinotecan 10mg/kg

Tumor Measurements 2x/week

Study Start — **Treatment** — **Day 21**

SP16 showed no interference with the effects of the **chemotherapy drug**, Irinotecan, in a **tumor xenograft model** of pancreatic cancer (BXPC-3 cells). Mice treated with irinotecan (10mg/kg) and a very high dose of SP16 (**5x higher than the effective dose**) simultaneously

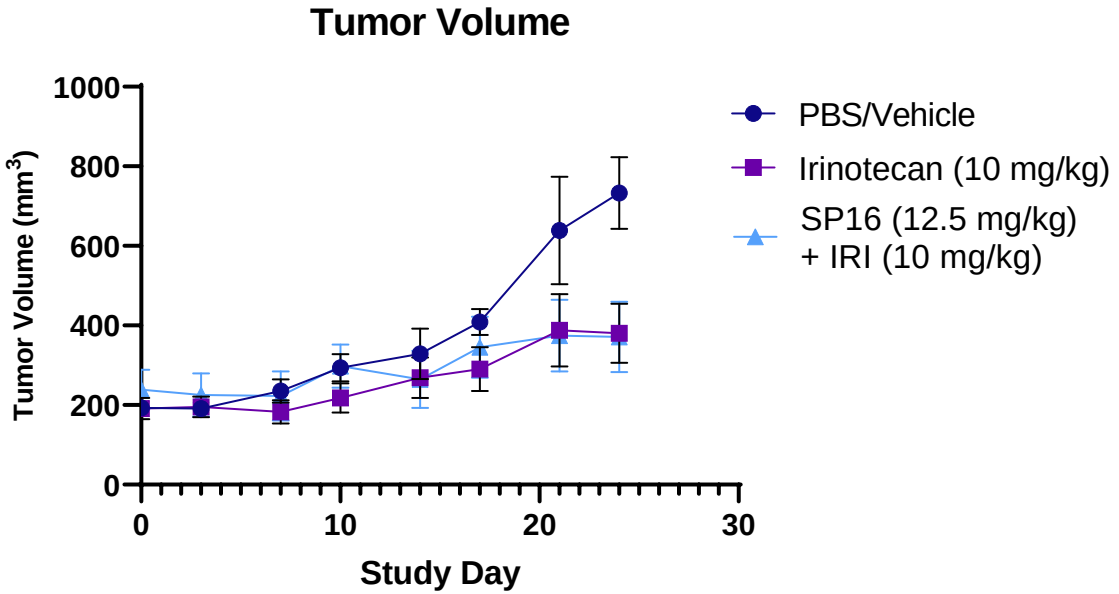


Fig. BXPC3 pancreatic cancer cells (5x10^6) were implanted into the flanks of nu/nu (nude) mice. Mice were treated with respective treatments once tumors reached an average of ≥200 mm^3. Mice were treated for 5 consecutive days the first week and then 3x/week for the next two weeks. Tumor volumes were measured twice per week for 21 days.

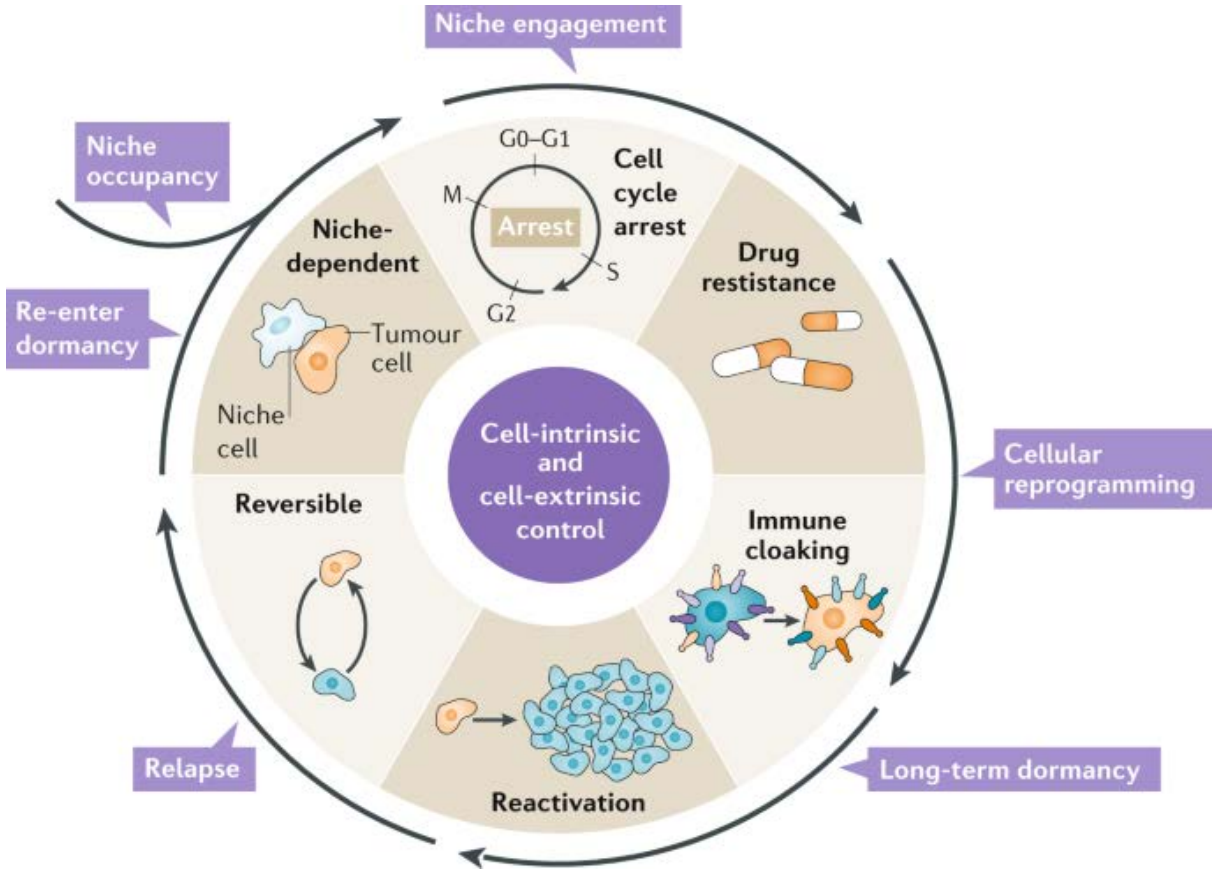
Clinical plan in CIPN:

- **Patient population:** Cancer patients with solid tumors treated with taxane or platinum agents (breast cancer, ovarian cancer or colorectal cancer).
- **Treatment Regimen**: SP16 (0.2 mg/kg) given IV with at least 3 rounds of chemotherapy to prevent peripheral neuropathy
- **Primary Endpoint**: Safety and tolerability of SP16 and prevention of the development of CIPN (based on PROs, ClinROs, and functional tests)

Tumor Dormancy

Cancer cells are extraordinarily heterogeneous in the tumor microenvironment.

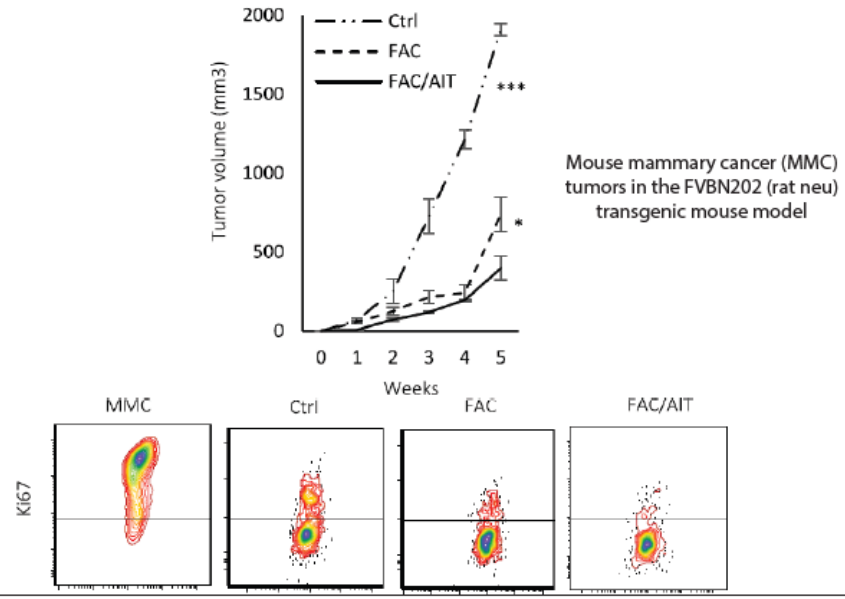
- A subset of cells exhibit low or no proliferation and are highly sensitive to adverse environmental cues, including from the immune system or chemotherapy.
- In response to these adverse signals, these cells enter a quiescent, non-proliferative state characterized by arrest in the G_0/G_1-S. transition.
- Characteristics of these dormant cancer cells (DCCs) include:
  - Highly resistant to chemo/radiotherapy;
  - Recalcitrant to extrinsic apoptosis inducers;
  - Express high levels of PD-L1;
  - And are epigenetically poised for a switch to proliferative, tumor-forming phenotype.



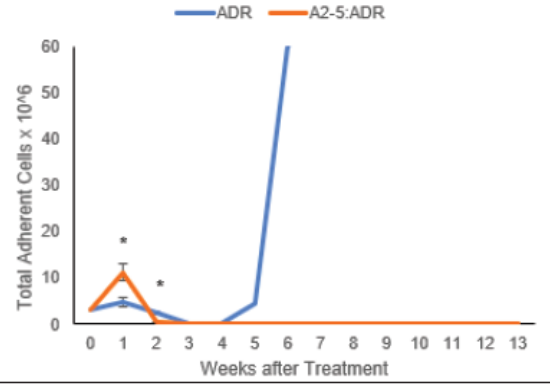
LRP1 agonists prevent reactivation of dormant cancer reservoirs

- In collaboration with Dr. Manjili at VCU, the effects of an SP16 derivative on tumor dormancy was tested in a mouse mammary cancer (MMC) model.
- Both chemotherapy and immune checkpoint inhibitors can induce DCC selection.
  - On the right, FAC (5-FU, Adriamycin, and cyclophosphamide) and anti-PD-1 (AIT) drive tumor dormancy (Aqbi et al. 2020).
  - SP16 analog (A2.5) prevents cells from exiting the dormant state, rendering quiescent reservoirs utterly inert.

Chemotherapy (FAC) and combined chemotherapy/immunotherapy (FAC/AIT) reduce tumor growth but drive dormancy



An SP16 derivative prevents dormancy reversal, locking DCCs into a non-proliferative state



Conclusions

SP16 shows neuroprotective, anti-inflammatory and analgesic effects in preclinical models of pain and nerve injury

- SP16 promotes primary adult sensory neuron outgrowth
- The increase in neurite length is associated with an increase in RAGs (Regeneration Associated Genes)
- SP16-induce cell signaling is LRP1 dependent in neuron-like cells (PC12)
- SP16 modulates pain related behaviors in 3 preclinical rodent models of pain: acute nociceptive (capsaicin), acute tissue injury-induced (formalin) and neuropathic pain (PNL)
- Molecular mechanisms include regulation of innate immunity (Toll-like receptor 4) in nerves and recruitment of inflammatory cells (CD11b+) cells into both cell bodies and nerves after injury

Management, Board & Scientific Advisors

Experienced Management Team

Cohava Gelber
PhD, MBA - Founder, President & CEO
Executive positions in biopharmaceutical companies (ImmuLogic Pharmaceutical Corporation, Molecular Discoveries, MannKind, ATCC). Weizmann Institute (PhD), Stanford University (Post Doc), Cornell University (MBA)

Larry Douglas Altstiel
MD, PhD– Acting CMO - Scientific Advisory Board Member
Former senior executive in Pfizer and Lilly Drug Development. Dr. Altstiel is a neurologist by training and focused his PhD on cell biology, virology and physical chemistry

Raffi Mikaelian
MS, VP Drug Development
Former executive positions with responsibility for business development and both preclinical and clinical project management. Experience in inhalation (environment and drug), infusion/IV, general toxicology/ADME/discovery/animal modes & safety pharmacology.

Dana Austin
PhD, VP Research & Development
Lead researcher for SP-16, dedicated to the development of peptide drugs as therapeutics. Unique background includes veterinary medicine, infectious disease, and Army medical laboratory research. MS, Microbiology and Infectious Disease, George Mason University.

Halle Raisigel
VP of Operations & Corporate Affairs
Entrepreneur with eighteen years executive, marketing and project management experience. Graduate of Western Michigan University and US Army Veteran.

Scientific Advisors

Jerome Zeldis
MD, PhD

Dr. Zeldis is the former Chief Medical Officer of Celgene Corporation (Nasdaq:CELG). Dr. Zeldis has played an instrumental role at the company, helping it grow into one of the largest global pharmaceutical firms.

Marc Rothenberg
MD, PhD

Director, Division of Allergy and Immunology; Director, Cincinnati Center for Eosinophilic Disorders; Professor, UC Department of Pediatrics

Gordon Smith
MD, FAAN

Chair, Department of Neurology. VA Commonwealth University

Jonathan Zenilman
MD

The Chief of the Division of Infectious Diseases at Johns Hopkins Bayview Medical Center since 2003. Under his leadership, the Bayview division has developed major clinical and research programs in STIs, hospital epidemiology, antibiotic stewardship and skin and soft tissue infections.

Antonio Gotto
MD

Previous Dean of Weill Medical College of Cornell University. Prior to his appointment he was chairman of the department of internal medicine at Baylor College of Medicine for 20 years. Dr. Gotto has been National President of the American Heart Association and President of the International Atherosclerosis Society. He is best known for his research into blood lipids.

Alexander Fleming
MD

Co-Founder of Kinexum LLC – a leading strategic consulting organization in the cardiometabolic space. Serves on over a dozen clinical advisory boards for major pharma and biotech companies. Former Head of Metabolic Group, FDA

Wendy Campana
PhD

Co-Director of CRG-STEMM and Professor of Anesthesiology and a member of the Program in Neurosciences at the University of California San Diego. Dr. Campana's work focuses on cellular and molecular mechanisms of peripheral nerve injury and how injury is associated with chronic neuropathic pain.

Lawrence Steinman
MD

Professor of Neurology and Neurological Sciences, Pediatrics, and Genetics at Stanford University. Dr. Steinman holds a number of patents in the areas of immunology, and for therapies of Huntington Disease, type 1 diabetes and MS.

Board of Directors

Cohava Gelber, PhD, MBA
Chairperson
Executive positions in biopharmaceutical companies (ImmuLogic Pharmaceutical Corporation, Molecular Discoveries, MannKind, ATCC). Weizmann Institute (PhD), Stanford University (Post Doc), Cornell University (MBA)

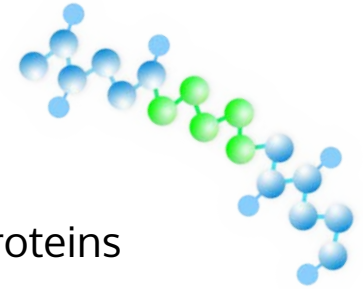
John Abeles, MD
Board Member
Senior Medical Executive with Sterling Drug, Pfizer, Revlon Health Care, and Health Care Analyst at Kidder Peabody. Entrepreneur, venture investor and executive board in dozens of successful companies

Joel Kanter
Board Member
Has served as President of Windy City, Inc., a privately held investment firm, since July 1986. Mr. Kanter has been instrumental in the formation, and financing of multiple companies among them Prolor Biotech (acquired by Opko for ~$450M) and Medgenics, Inc. (MEDG: NYSE Amex)

David Dove, MD, MBA
Board Member
Executive and board positions in biopharmaceutical companies (Advanced Biohealing, Aeris Therapeutics). New York University (MD) UC Berkeley (MBA

Guy Yachin, Eng, MBA
Board Member
Founder and chairperson of multiple biomedical companies (Chiasma, Enzymotec, MGVS, Remon, Nanopass). Technion – Israeli Institute of Technology (BSc., MBA)

Summary



- Platform of **first-in-class** peptide therapeutics derived from naturally occurring tissue protecting proteins (SERPINS)
- The **unique** mechanism of action of **Lead Drug (SP16)** is very well defined, it is homeostatic and **non-immunosuppressive**
  - Targets **LRP1** and shuts down inflammatory pathways **(inflammasome)** and activates cell survival pathways
- Risk is mitigated as a bio-superior to widely researched and safely used generic drug
  - Modified to increase stability and potency
- SP16's **anti-inflammatory and protective effects** have been **validated** in numerous disease models with KOL collaborators
  - Completed **Phase 2A** trial as an adjunctive treatment to reduce Acute Myocardial Infarction (AMI) mediated inflammation and heart injury; manuscript of Phase 2A trial and editorial published (July 2022)
  - Current Phase 2 trial at University of VA treating hospitalized COVID 19 patients with SP16
- Strong IP covering **composition of matter** and **use**
- Can be applied for the treatment of numerous human diseases with underpinning inflammatory responses; **Large market potential**

For more information contact

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