Yale University Innovation Pipeline

Biomedical

YALE VENTURES

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Oncology

YV9069: Dual MIF - D-DT Targeting to Enhance Immunotherapy Responses

Principal Investigator: Thuy Tran, MD, PhD and Richard Bucala, MD, PhD

Background:

- Limited immune therapy options result in ~58% best response, with resistance and toxicity affecting outcomes.
- Checkpoint inhibitors target few pathways and offer limited standard options after progression.
- Dual targeting of MIF and D-DT enhances immune therapy response, overcoming resistance.

Indications: Melanoma, colorectal cancer (CRC), glioblastoma (GBM), head and neck squamous cell carcinoma (HNSCC).

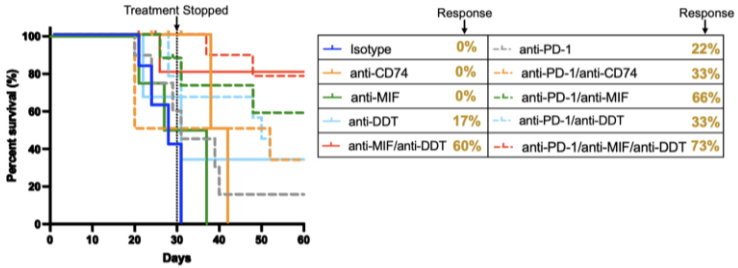
Innovation & Asset:

- **Dual Inhibition**: Simultaneous targeting of MIF and D-DT fully blocks signaling and boosts cancer responses.
- **Improved Immune Infiltration**: Enhances cDC1 and increases Th1 cytokines. Enhances gene sets for antigen processing and presentation in monocytes/macrophages.
- **Tumor Agnostic**: Effective in melanoma, CRC, GBM, and HNSCCs.
- **Complementary Approach**: Synergizes with existing checkpoint inhibitors (e.g., anti-PD-1).
- **Validated Antibodies**: High-affinity, preclinical anti-MIF and anti-D-DT monoclonal antibodies available. Ongoing need for antibody engineering of humanized, dual-targeting antibody for trials.

IP: U.S. Patent filed

Learn More: Yale Life Sciences PitchFest

Enhanced Survival with Dual MIF/D-DT Targeting and PD-1 Blockade



The Kaplan-Meier survival curve demonstrates improved survival rates in preclinical models with combination therapy. Dual targeting of MIF and D-DT resulted in a 60% response rate and improved survival, which was further enhanced by adding anti-PD-1. Results are superior to single or combined with PD-1 inhibition and superior to blocking the MIF/D-DT receptor, CD74. This highlights the efficacy of MIF/D-DT pathway inhibition in overcoming immune resistance and enhancing tumor response.

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YV8983: BIOACTIVATED CYTOTOXINS FOR TARGETED CHEMOTHERAPY

Principal Investigator: Seth Herzon, PhD

Background:

- Antibody-drug conjugates (ADCs) have received >$3B investment since 2022 alone, but the MTD of ADCs rarely exceeds conventional chemotherapies.
- Current ADC payloads are pan-cytotoxic, difficult to optimize, and lack tumor-specific targeting.
- This technology introduces DNA Self-Activating Warheads (SAWs) for ADCs, enhancing tumor specificity and safety.

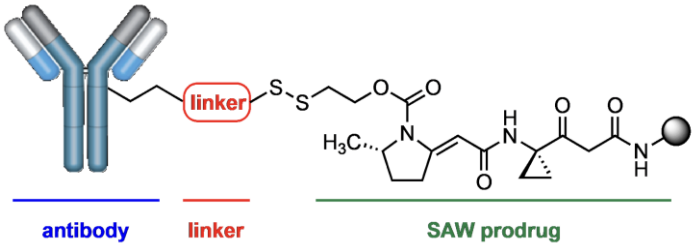
Innovation & Asset:

- **Selective Action:** SAWs act as unreactive prodrugs, activating only in tumor cells.
- **Enhanced Safety:** Tumor-restricted genotoxins reduce off-target toxicity.
- **Scalability:** Modular SAW design allows easy synthesis and optimization.
- **Customizable MOAs:** Control DNA damage mechanisms (monoalkylation, cleavage, cross-linking) for tailored therapies.
- **Strong IP and Pipeline Potential:** Platform de-risked through Blavatnik-funded preclinical proof-of-concept studies.

IP: Patent application not filed.

Learn More: Yale Life Sciences PitchFest

Modular Design of SAW Technology for ADC Development



This schematic illustrates the SAW (Selective Antibody Warhead) platform, enabling versatile antibody-drug conjugates (ADCs) with optimized properties and controlled mechanisms of action. The system consists of three key components: an antibody (blue), a linker (red), and a SAW prodrug payload (green). This modular approach allows fine-tuning of drug properties and tailoring of mechanisms of action to exploit tumor-associated DNA repair defects, enhancing targeted cancer therapy.

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YV8826: Rosevix (Rosziqumab) A ROS1 Biologic for Invasive Cancers

Principal Investigator: Daryl E. Klein, MD, PhD

Background:

Invasive Lobular Carcinoma (ILC) affects ~44,000 people in the U.S. annually; Oral Squamous Cell Carcinoma (OSCC) is the most common head and neck cancer with ~61,000 cases annually.

Available targeted therapies, such as kinase inhibitors, lack specificity, have high toxicity, and face resistance issues.

ROZIQUMAB, the first ROS1-specific biologic, designed for precision targeting of ROS1-driven invasive cancers.

Indications: Invasive Lobular Carcinoma (ILC), Oral Squamous Cell Carcinoma (OSCC), Hereditary Diffuse Gastric Cancer (HDGC), ROS1-positive cancers

Innovation & Asset:

First-in-Class Biologic: World's first ROS1-specific monoclonal antibody (mAb) biologic.

Precision Targeting: High specificity for ROS1 reduces off-target toxicity and resistance.

Proven Structural Insights: High-resolution ROS1 structure solved, enabling precise design and activity validation.

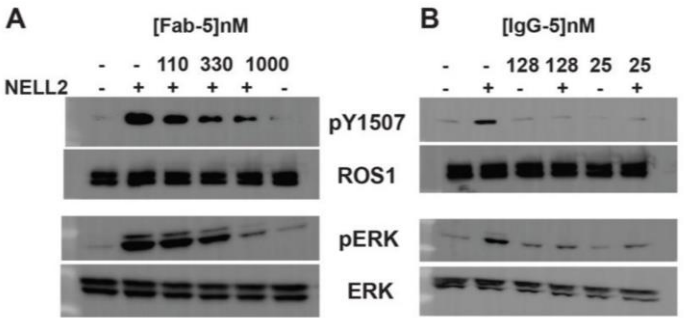
Therapeutic Versatility: Adaptable for Antibody-Drug Conjugate (ADC) therapies to enhance efficacy.

Improved Safety Profile: Lower general toxicity compared to small-molecule kinase inhibitors.

IP: US Patent filed

Learn More: Yale Life Sciences PitchFest

Fab-5 and its reformatted IgG-5 inhibit NELL2 induced activation of ROS1



A, Increasing amounts of Fab-5 show greater inhibition of NELL2 induced ROS1 and ERK activation. B, The reformatted full IgG antibody of Fab-5 (IgG-5) displays potent inhibition of NELL2 induced activity

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YV8604: Novel Methods of CAR-T Improvement

Principal Investigator: Xiaolei Su, PhD

Background:

- Chimeric Antigen Receptor T (CAR-T) cell therapy's low antigen sensitivity limits efficacy in high antigen cancers, leading to increased relapse rates.
- Current CAR-T cells struggle with low antigen sensitivity, reducing their therapeutic effectiveness and increasing the likelihood of cancer relapse.
- This novel technology enhances the sensitivity and efficacy of CAR-T cells through the fusion of a specific group of motifs to existing CARs.

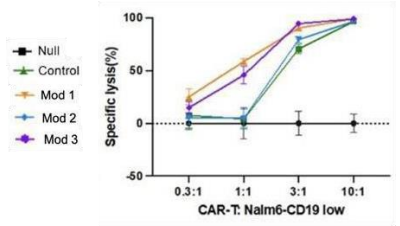
Indications: CAR-T therapy improvement

Innovation & Asset:

- **Enhanced Sensitivity:** Sensitization of CAR-T cells via novel motif fusion.
- **Broad Application:** Applicable to any existing CAR structure.
- **Proven Efficacy:** Demonstrated increased in-vitro cytotoxicity in multiple cancer cell lines.
- **In Vivo Success:** Enhanced tumor inhibition in xenografted mouse models.
- **Stable Performance:** No change in T-cell exhaustion markers compared to unmodified CAR-T cells.

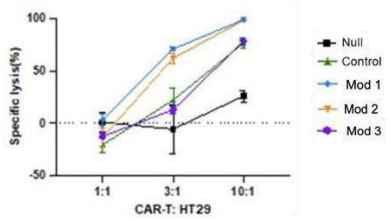
IP: PCT/US2024/012029

A



Compared to control CD19 CAR-T, modifications 1 and 3 led to significantly improved cytotoxicity against CD19-low Nalm6 cells (B-ALL).

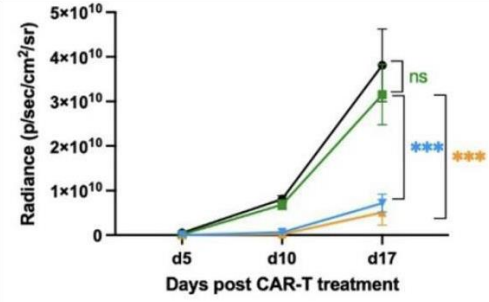
B



Compared to control HER2 CAR-T, modifications 1 and 2 led to significantly improved cytotoxicity against HT29 cells (colorectal adenocarcinoma).

C

Mice were injected with Nalm6 cells (B-ALL), then treated with an infusion of either PBS, control CD22 CAR-T cells, or modified CD22 CAR-T cells. Compared to control CAR-T cells, both modifications 1 and 3 resulted in significantly improved tumor inhibition as measured by Luciferase assays.



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YV8476/6265: Antibody for Cancer Immunotherapy

Principal Investigator: James Hansen, MD, MS

Background:

- Cyclic GMP-AMP synthase (cGAS) stimulates immunity via the STING pathway in response to cytoplasmic DNA
- STING activation inhibits tumor immune evasion

Indications: Cancer Immunotherapy (primary indication: glioblastoma multiforme [GBM])

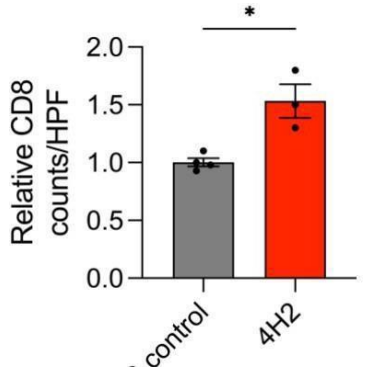
Innovation & Asset: Cytoplasmic anti-Guanine antibody, 4H2:

- Activates STING pathway signaling via cGAS
- Improves cytotoxic T-cell infiltration into orthotopic tumors in mouse model of GBM (A)
- Prolongs survival in mouse model of GBM (B)

IP: 63/379,123 filed 10/11/22, PCT/US2023/076605 filed 10/11/23

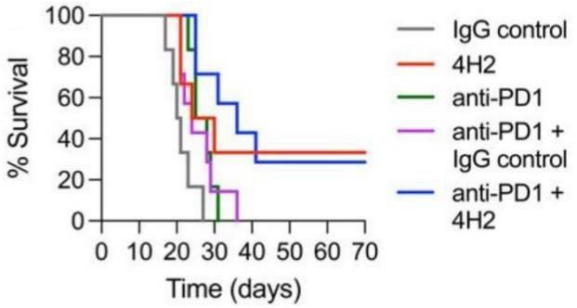
A

In mouse brain glioblastoma multiforme sections, administration of 4H2 significantly increases relative counts of CD8+ T-cells when compared to an IgG control, demonstrating its immunostimulatory effect.



B

Kaplan-Meier plot demonstrates that 4H2 administration improves survival in mice with GL261-derived orthotopic GBM tumors both as a monotherapy and in combination with PD1 blockade.



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YV8466: Targeting Virally-Driven Cancer with an mRNA Vaccine

Principal Investigator: Jeffrey Ishizuka, MD, DPhil

Background:

- Aggressive, frequently lethal malignancy with a high proportion of cases attributable to viral infections.
- Current therapies are limited in effectiveness for virally-driven cancers.
- This technology uses a novel mRNA vaccine to target oncogenic, virally-encoded antigens, improving treatment outcomes.

Indications: Virally-mediated malignancy

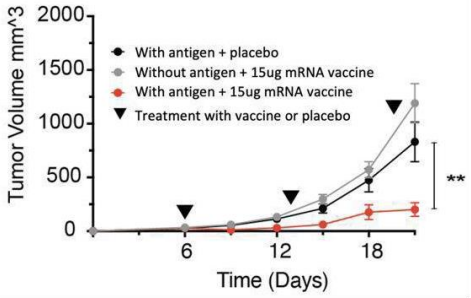
Innovation & Asset:

- **Novel Vaccine:** mRNA vaccine targeting oncogenic viral antigens.
- **Proven Efficacy:** Reduces tumor burden and increases survival in mouse models.
- **Immunogenic Response:** Enhances T-cell-driven immune response against cancer cells.
- **Versatility:** mRNA approach offers flexibility, improved immunogenicity, and cost-effective synthesis.

IP: PCT/US2023/084086

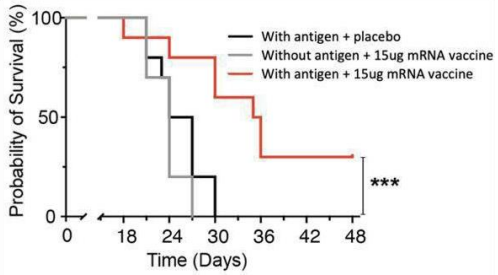
A

Vaccine administration significantly reduces tumor volume in mouse models of cancer expressing the targeted viral antigen



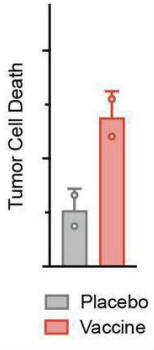
B

Vaccine administration significantly increases survival in mouse models of cancer expressing the targeted viral antigen



C

Vaccine transfection into patient-derived Mo-DCs expands patient-derived T cells and enhances killing of matched patient-derived tumor cells.



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YV8209: Novel Methods of Inducing Programmed Cell Death in Tumor Cells

Principal Investigator: Laura Niklason MD, PhD and Mehmet Kural, PhD

Background:

- Fas is a transmembrane death receptor that transduces programmed cell death upon binding to its ligand.
- Insufficient expression of these receptors on the cell surface makes cancer cells insensitive to the Fas-induced killing.

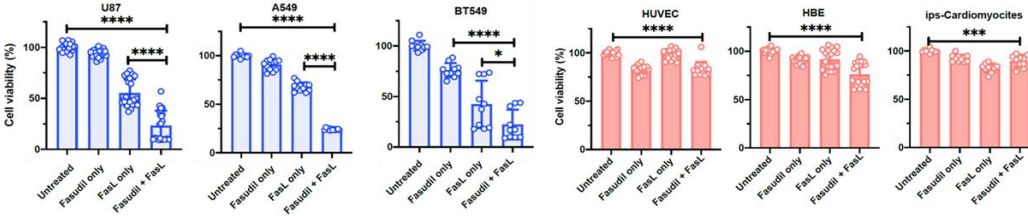
Indications: Anti-tumor drug combination that spares non-cancerous cells.

Innovation & Asset:

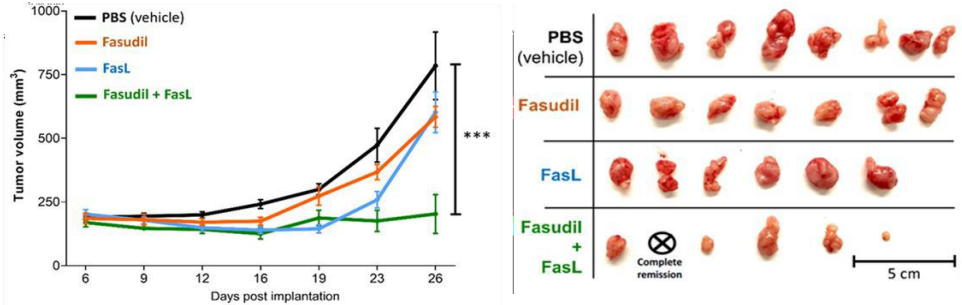
- **Tumor sensitivity:** Sensitization of tumor cells by increasing surface receptor expression.
- **In vitro efficacy:** Demonstrated strong cytotoxicity in multiple cancer lines.
- **Selective targeting:** Spares non-cancerous cells such as cardiomyocytes, endothelial, and bronchial epithelial cells.
- **In vivo success:** Potent tumor inhibition shown in xenograft glioblastoma model in nude mice.
- **Therapeutic promise:** Potential alternative to chemotherapy with milder side effects.

IP: US patent filed: 18/687,104

Fas ligand and Fasudil combination has potent cytotoxic effect on in various cancer cells lines, U87, PC3, BT549, A549, HepG2 and SUM159 (Blue bars). Noncancerous endothelial cells (HUVEC) cardiomyocytes and bronchial epithelial cells (HBE) were not dramatically affected as cancer cells.



Fas ligand and Fasudil combination therapy showed potent anti-tumor effect in nude mice with xenograft glioblastoma.



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YV7950: Novel Small Molecule Inhibitor for Treatment of PARP inhibitor-Resistant Ovarian Cancer DB4

Principal Investigator: Elena Ratner, MD, MBA

Background:

- Ovarian cancer affects over 21,000 women annually in the U.S., with 50% showing no HR deficiency and resistant to PARP inhibitors.
- Current treatments using PARP inhibitors are ineffective for HR repair proficient cancers and face resistance in previously sensitive cancers.
- DB4, a novel small molecule inhibitor, overcomes this by blocking HR repair and sensitizing resistant cancer cells to PARP inhibitors.

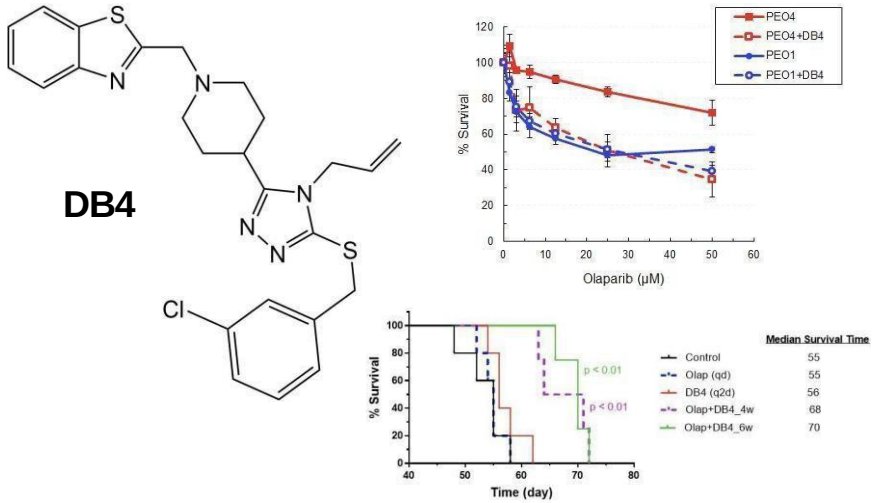
Indications: Ovarian Cancer, Breast Cancer

Innovation & Asset:

- **Novel Approach:** DB4 targets HR repair in PARPi-resistant cancer cells.
- **Combination Therapy:** Enhances efficacy of existing PARPi therapies like olaparib.
- **Effective in Vivo:** Significantly prolongs survival in mouse models.
- **Potential IP:** Patent application pending for unique inhibitor.
- **Clinically Relevant:** Addresses a significant unmet need in ovarian cancer treatment.

IP: US patent filed: 18/555,112

Reference: Lin et al., Sci Rep. 2021 Apr 13;11(1):8042.



Figures demonstrating the efficacy of combining DB4 and the PARPi olaparib to treat PARPi-resistant ovarian cancers. **Top,** DB4 rendered PARPi-resistant PEO4 ovarian cancer hypersensitive to olaparib similar to PARPi-sensitive PEO1 ovarian cancer in culture. **Bottom,** mice were implanted with PARPi-resistant PEO4 ovarian cancer xenografts and treated with olaparib, DB4, and both concurrently. PEO4 xenografts developed ascites and the survival time of mice were determined. The combination of DB4 and olaparib significantly prolonged the survival time of mice while either drugalone had no effects compared with vehicle-treated control mice.

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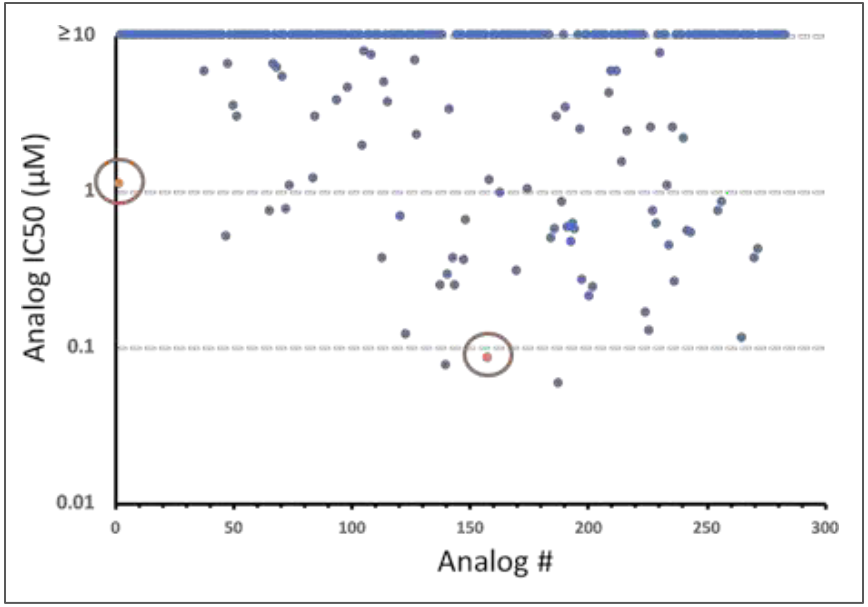
YV7888: First in Class Glycosylation Inhibitors for the Treatment of Cancer

Principal Investigator: Joseph N. Contessa, MD, PhD

Background: Cancer patients with receptor tyrosine kinase (RTK) activating mutations benefit from RTK-targeted therapies, but frequently develop resistance to treatment. Researchers at Yale have pioneered glycosylation inhibitors that block RTK signaling.

Indications: Tumors driven by RTK mutations, including non-small cell lung cancer, colon cancer, head and neck cancer, and breast cancer. Possibly additional indications.

Innovation: Novel small molecule inhibitors of oligosaccharyltransferases (OST) with IC_{50}'s below 100 nM.



IP: US patent Application US20240010641A1

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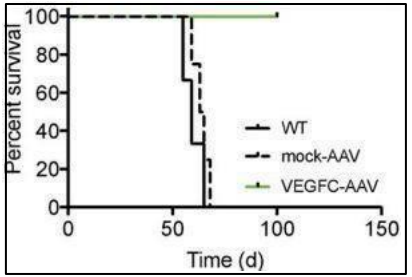
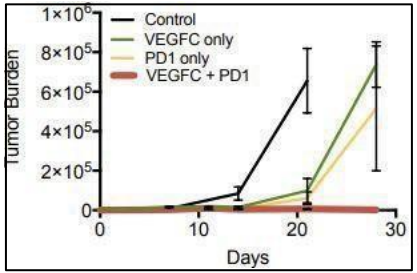
YV7502: Vascular Endothelial Growth Factor C (VEGF-C) to treat Glioblastoma (GBM)

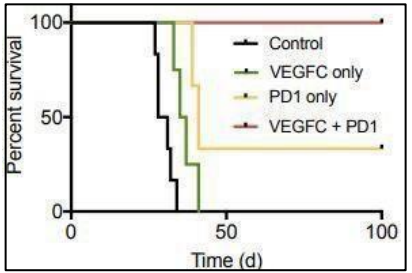
Principal Investigator: Eric Song, MD, Ph.D.

VEGF-C potentiates immunotherapy to eradicate GBM

- Unlike VEGF-A, VEGF-C promotes **lymphangiogenesis**
- VEGFC-AAV pre-treatment in mice results in complete rejection of brain tumors.
- VEGFC-mRNA treatment after tumor establishment potentiates anti-PD1 therapy in mice, results in 100% survival
- Lower tumor burden correlates with higher survival in mice







IP: WO 2020/102627 A2

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YV7358: Targeting of ARID1A-deficient cancers by exploiting a newly identified metabolic vulnerability

Principal Investigator: Gloria-Huang, MD, FACOG

Background:

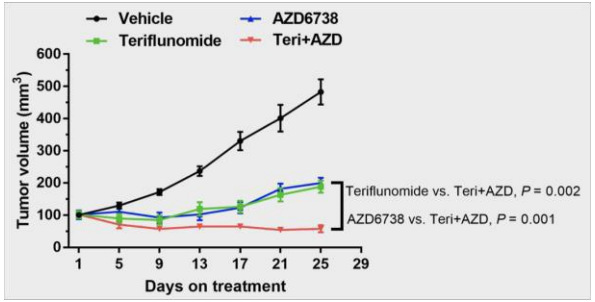
- ARID1A gene mutations occur in approximately 35-55% of endometrial and non-serous ovarian cancers.
- Current therapies are limited in effectiveness against ARID1A-mutated cancers.
- This new technology identifies metabolic vulnerabilities in ARID1A-mutated cancers, targeting them with inhibitors of de novo pyrimidine synthesis.

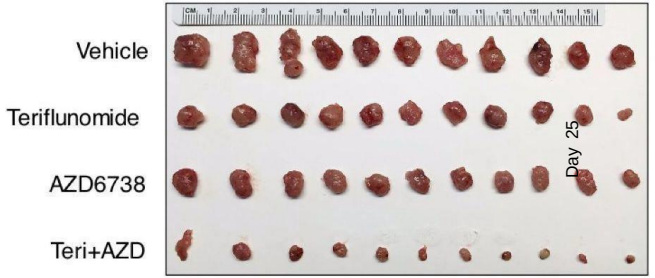
Indications: Endometrial Cancer, Non-Serous Ovarian Cancer

Innovation & Asset:

- **Metabolic Targeting:** Exploits ARID1A-mutated cancer's sensitivity to pyrimidine synthesis inhibitors.
- **Synergistic Therapy:** Combination with DNA damage repair inhibitors enhances efficacy.
- **Tumor Regression:** Demonstrated tumor regression in PDX models.
- **Patent Pending:** Intellectual property secured with a pending US patent application.
- **Clinical Potential:** Offers a novel approach to treat ARID1A-deficient cancers.

IP: US Patent:11,801,232





Figures show ing the effect of a novel combination treatment for ARID1A-mutated cancers. Mice w ere implanted with patient-derived xenografts from a patient w ith ARID1A-mutated ovarian cancer. After PDX establishment, animals were treated with a pyrimidine synthesis inhibitor (teriflunomide), a DNA damage repair inhibitor (AZD6738), or both concurrently, and PDX grow th compared to vehicle-treated animals. While either inhibitor alone effectively suppressed proliferation, only the combination treatment resulted in sustained tumor regression.

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YV7119: Nanomaterial Technology to Enable Efficient Oral Drug Delivery

PARTNERED

Principal Investigator: Jiangbing Zhou, PhD

Background:

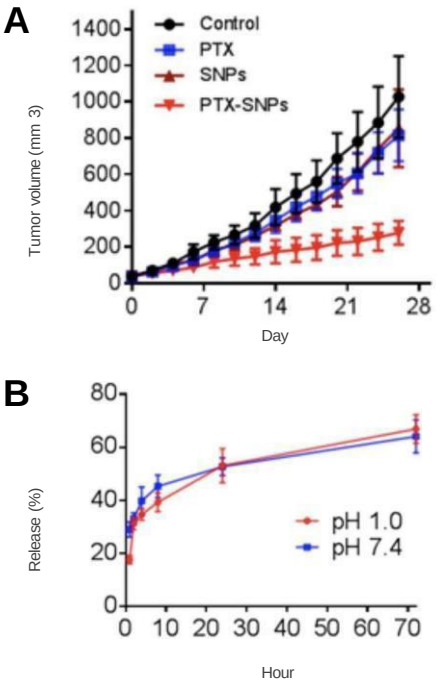
- Oral drug delivery is challenged by the gastrointestinal tract's harsh acidic environment, limiting the bioavailability of many therapeutic compounds.
- Existing methods often fail to deliver sufficient plasma concentrations of drugs through oral administration.
- This technology utilizes Supramolecular Nanoparticles (SNPs) to enhance the oral bioavailability of various cargo drugs, including chemotherapeutic agents and peptide therapeutics.

Indications: Tumors, Diabetes, Stroke

Innovation & Asset:

- **Advanced Nanotechnology:** SNPs enhance the oral bioavailability of drugs.
- **Stability:** Functional nano- and microstructures are stable in strong acidic environments (down to pH 1.0).
- **Effective Penetration:** Efficiently penetrate the gastrointestinal tract.
- **Enhanced Efficacy:** Greater plasma concentration and targeted tissue adsorption following oral administration.
- **Broad Application:** Demonstrated strong efficacy in treating tumors, diabetes, and stroke in animal models.

IP: US patent: 11,478,433



Enhanced bioavailability and stability of orally delivered drugs.

(A) Oral administrated drug paclitaxel (PTX)-SNPs reduced tumor volumes substantially compared to control group, free PTX, and empty SNPs.

(B) Exposure to pH 1.0 did not change the release of PTX from SNPs.

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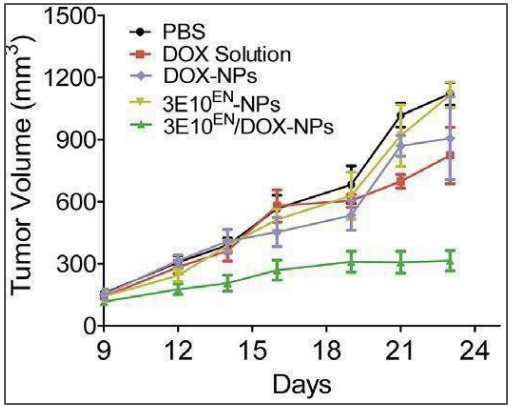
YV7013: Anti-DNA Antibody for Targeted Delivery to Tumors

PARTNERED

Principal Investigator: James Hansen and Jiangbing Zhou

Circulating autocatalytic anti-DNA antibody 3e10

- **Background:** A key feature of the tumor microenvironment, compared to healthy tissue, is the presence of a comparatively larger amount of extracellular DNA from actively dividing, apoptotic or necrotic tumor cells.
- Circulating anti-DNA autoantibody 3e10 penetrates cell nuclei. When it is conjugated to the surface of nanoparticles, it targets the nanoparticles to the extracellular DNA in the tumor environment.
- The conjugate works in an autocatalytic manner that increases in efficiency with time and treatment.
- **IP status.** US patent 11,590,242 issued 2/28/2023
- **Reference:** Chen et al. (2016) Oncotarget



Synthesized DOX-loaded PLGA nanoparticles with surface conjugated 3E10EN have a significantly greater effect on tumors than DOX-NPs or DOX alone.

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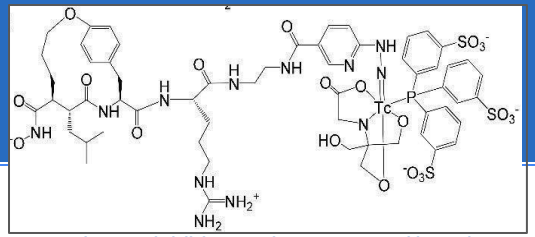
YV6966: MMP-based Inhibitors and Tracers

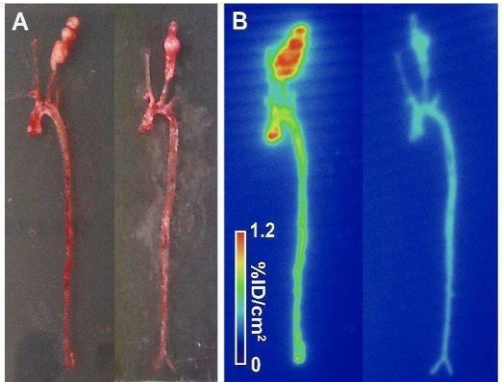


Novel MMP inhibitor and MMPtargeted imaging tracer ^{99m}Tc-RYM1

Principal Investigator: Mehran Sadeghi, PhD

Novel matrix metalloproteinases (MMPs) Inhibitor and MMP-targeted imaging tracers

- Upregulation of MMPs is associated with a wide range of diseases including cancers, inflammation and cardiovascular diseases.
- Measurement of MMP expression and activation in vivo could enable physicians to accurately diagnose and treat MMP-associated diseases.
- Currentlythere are no tracers available in the clinic for imaging MMP activity.
- A new type of a MMP inhibitor (1) has been developed, which also serves as a versatile scaffold (3) for developing MMP-targeted imaging agents.
- Additionally, a novel precursor was also designed as a parent building block for making different type of hydrophilic MMP imaging tracers.
- These novel scaffolds displayimproved pharmacokinetics and water solubilityas compared to previously reported MMP SEPCT probes (i.e.RP805)
- **IP status:** issued US patent: 11,286,251



^{99m}Tc-RYM1 imaging of carotidaneurysm

Ex-vivo photography (A) and autoradiography (B) of aortae and carotid arteries from apoE-/- mice with CaCl2-induced carotid aneurysm injected with 99mTc-RYM1w ithout(left) andw iththe pre-injectionof an excess of MMP inhibitor, RYM(right).

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YV6922: Selection of Non Small Cell Lung Cancer Patients Responsive to Checkpoint Inhibitors

Principal Investigators: Kurt Schalper, MD, PhD & David Rimm, MD, PhD

Background:

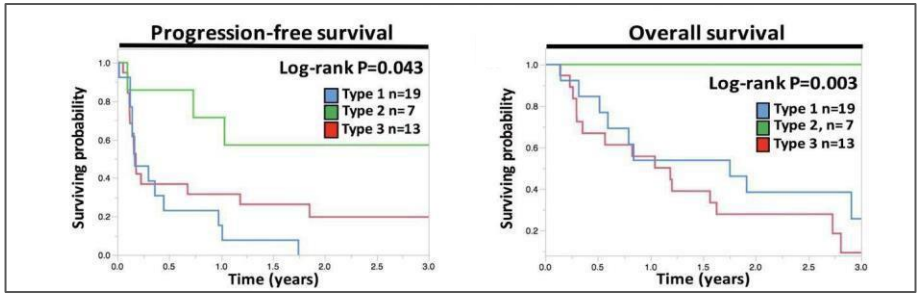
- Tumor-Infiltrating Lymphocytes (TILs) can predict responses to Checkpoint Inhibitor therapy in NSCLC, which affects millions.
- Existing methods for evaluating response to therapy lack precision in identifying dormant TIL phenotypes.
- New quantitative immunofluorescence method accurately identifies TIL phenotypes that correlate with clinical response to therapy.

Indications: Non-Small Cell Lung Cancer (NSCLC), Checkpoint Inhibitor therapy

Innovation & Asset:

- **Precision Biomarkers:** Identifies TIL phenotypes (high CD3, low Granzyme B, low Ki67).
- **Predictive Value:** Correlates with clinical response to therapy.
- **Enhanced Selection:** Helps in selecting patients likely to benefit from therapy.
- **Improved Outcomes:** Potential for better therapeutic results.

IP: US Patent: 11,644,467



Kaplan-Meier graphical analysis of 3-year progression free survival and overall survival of lung cancer cases treated with immune checkpoint blockers according to their TIL phenotype panel:

Type 1: Low CD3
Type 2: High CD3 + Low Granzyme B + Low Ki67
Type 3: High CD3 + High Granzyme B OR High Ki67
The number of cases in each group and the log-rank P value is indicated in the chart.

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YV6886: Novel Cancer Biomarker and Target

Principal Investigator: Andrew Xiao, PhD

Background:

- Oral drug delivery is challenged by the gastrointestinal tract's harsh acidic environment, limiting the bioavailability of many therapeutic compounds.
- Existing methods often fail to deliver sufficient plasma concentrations of drugs through oral administration.
- This technology utilizes Supramolecular Nanoparticles (SNPs) to enhance the oral bioavailability of various cargo drugs, including chemotherapeutic agents and peptide therapeutics.

Indications: Tumors, Diabetes, Stroke

Innovation & Asset:

- **Advanced Nanotechnology:** SNPs enhance the oral bioavailability of drugs.
- **Stability:** Functional nano- and microstructures are stable in strong acidic environments (down to pH 1.0).
- **Effective Penetration:** Efficiently penetrate the gastrointestinal tract.
- **Enhanced Efficacy:** Greater plasma concentration and targeted tissue adsorption following oral administration.
- **Broad Application:** Demonstrated strong efficacy in treating tumors, diabetes, and stroke in animal models.

IP: US Patent: 11,384,380

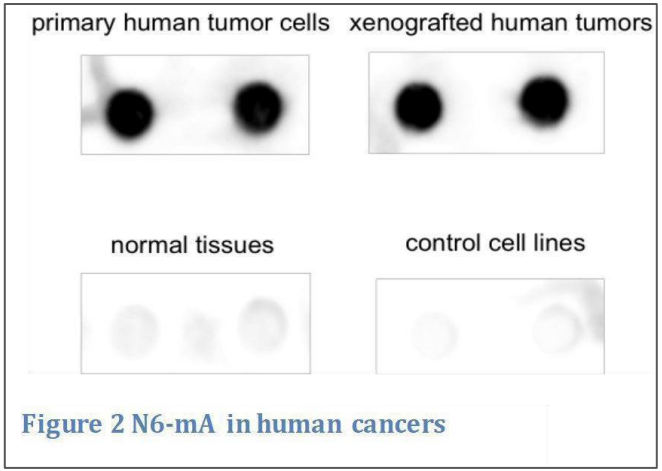

Figure 2 N6-mA in human cancers

Reference: Methylation on N6-adenine in mammalianembryonic stemcells. (2016) Nature 532, 329–333. doi:10.1038/nature17640.

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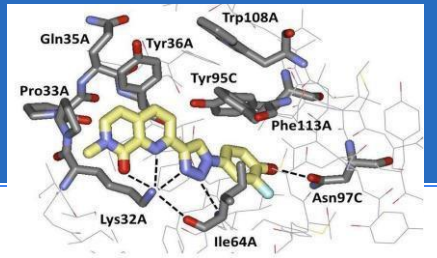
YV6558: Oncology/Inflammation Therapeutics



(a) Structure-based design with validated target

Principal Investigator: William Jorgensen

Background:

- Macrophage Migration Inhibitory Factor (MIF) is a pro-inflammatory cytokine and a clinically validated target for various cancer and inflammatory diseases.
- Current treatments using anti-MIF antibodies and MIF knockouts show in vivo activity but have limitations.
- New structure-based design of MIF antagonists provides highly potent, drug-like compounds with excellent metabolic stability.

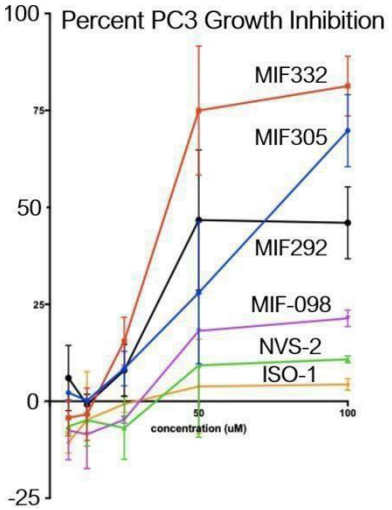
Indications: Cancer (prostate, colon, lung, melanoma), rheumatoid arthritis, sepsis, atherosclerosis, asthma, ARDS

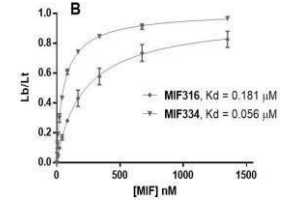
Innovation & Asset:

- **Highly Potent:** Two diverse series designed with ~1000x potency compared to other antagonists (a).
- **Extensive SAR Yield:** ~400 compounds with low nM MIF-binding.
- **Drug-Like Properties:** Economical synthesis routes and excellent metabolic stability.
- **Biological Activity:** Proven efficacy in PC3 prostate cancer cells (b).

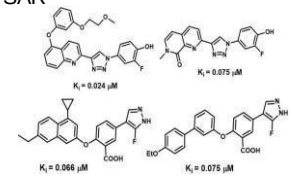
IP: Multiple national patents; US Patent 10,968,198

(b)





Novel/Improved Assays for SAR



Potent/Drug-like Leads

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YALE VENTURES

YV6325: Humanized Anti-DKK2 Clinical Candidates for Colorectal Cancer

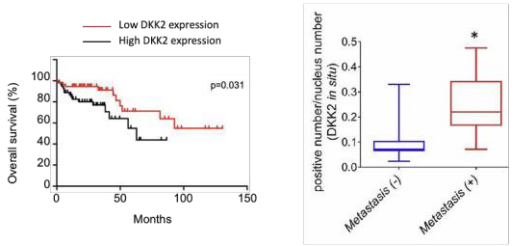
Principal Investigator: Dianqing (Dan) Wu, PhD

- **Background:** Why target DKK2
  - Upregulated in colorectal cancer (CRC) and associated with worse prognosis (**A**)
  - Involved in stemness, immune evasion, angiogenesis (**B**)
- **First Indication:** Microsatellite-stable colorectal cancer, including KRAS-mutant
- **Innovation:** First-in-class therapeutic
  - Validated in mouse models of CRC (**C**/**D**)
  - Three distinct MOAs (**B**)
  - Synergistic with standard of care (**D**)
  - No significant on-target toxicity in animal models(dns)
- **Assets:** Two humanized anti-DKK2 Clinical Candidates

IP: Broad coverage of compositions of matter & uses until 2036-39

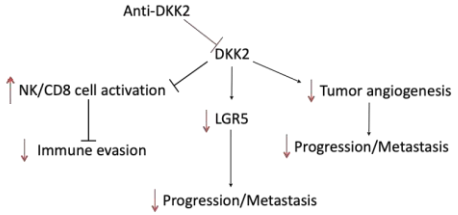
A

Left: High DKK2 expression is associated with lower survival in human CRC patients. Right: High DKK2 expression is associated with presence of metastasis in human CRC patients.



B

DKK2 acts via multiple independent mechanisms to promote cancer progression. Effects of anti-DKK2 shown in red.



C

Humanized anti-DKK2 shows identical anti-tumor activity compared to mouse anti-DKK2

D

Anti-DKK2 is synergistic with anti-VEGF treatment, a standard of care therapy in CRC

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YALE VENTURES

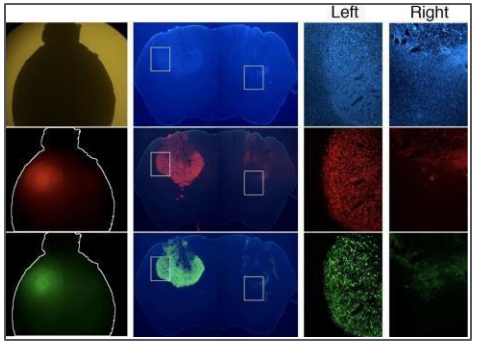
YV6290: An Oncolytic Virus for Treatment of Brain Cancers

PARTNERED

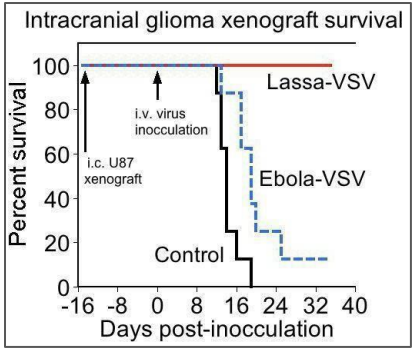
Principal Investigator: Tony Van Den Pol

Lassa-VSV is a superior safe oncolytic virus for treatment of braincancers

- Glioblastoma (GBM) are aggressive and invasive brain tumors that generallylead to death within a year of diagnosis.
- No cure exists for this form of cancer and current treatments onlyprolong life by a few months.
- Lassa-VSVis a novel recombinant oncolytic virus (OV) that can cross the blood brain barrier (BBB) and selectively kill glioma in the brain without the adverse effects of neurotoxicitythat is associated with other VSV-related OVs.
- In vivo mouse studies revealed selective infection and killing of GBM cells in the mouse brain after intravenous or intracerebral virus administration with substantially prolonged cancer survival far beyond that of control tumor-bearing mice that received no virus
- Lead Innovator: Anthonyvan den Pol, PhD



Intratumoral injection of Lassa-VSV (green) selectively infects and kills GBM cells (red) in the injected right tumor, and then migrates to the left tumor



Intravenously delivered Lassa-VSV crosses the BBB and protects mice from an implanted glioma

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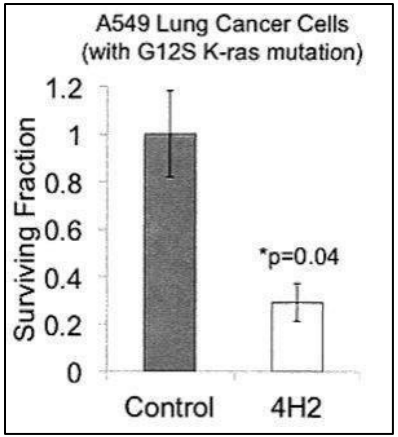
YALE VENTURES

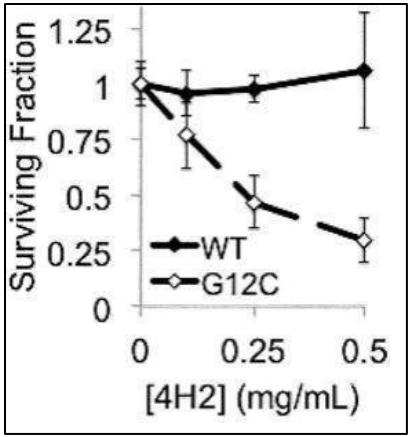
YV6265: Cell Penetrating Anti-Guanosine Antibody Therapeutic for Cancer with RasMutations

Principal Investigator: James E. Hansen, MD, MS

- **Background:** An antibody has been identified in a mousemodel of lupus with anti-guanosine activity and is capable of cellular penetration. This antibody has potential as a therapeutic agent for tumors driven by K-Ras. It can also be conjugated to a nanoparticle to deliver other therapeutics.
- **Indications:** Malignancies associated with mutant K-Ras
- **Innovation:** Cell penetrating antibody therapeutic, active against K-Ras
- **Issued Patents:** US 10,040,867 B2



4H2: exemplary Cell-penetrating anti-guanosine mAb



The surviving fraction of Cal12T cells without and with the G12C mutation in KRas, following exposure to mAb 4H2

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YV6056: RNA Hairpin Molecules as Immuno-oncology Agents

PARTNERED

Principal Investigator: Anna Pyle, Ph.D. and Akiko Iwasaki, Ph.D.

Background:

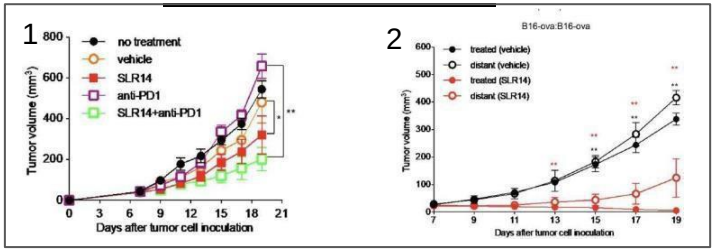
- Immunotherapy, like anti-PD1 therapy, is a promising cancer treatment but can benefit from agents that further enhance immune response.
- RNA hairpin molecules, such as SLR14, have been identified as potent stimulators of the immune system.
- This technology leverages SLR14 RNA to activate the RIG-I pathway, consistently inducing interferon production and enhancing tumor immune responses.

Indications: Immunotherapy, Cancer

Innovation & Asset:

- **Immune Activation:** SLR14 induces immune response through RIG-I activation.
- **Synergistic Therapy:** Enhances efficacy when combined with anti-PD1 therapy.
- **Demonstrated Efficacy:** Effective in mouse in vivo tumor models.
- **Abscopal Effect:** Exhibits systemic anti-tumor immunity beyond the primary tumor site.
- **Memory Response:** Induces long-lasting immune memory effects.

IP: US patent: 11,987,796



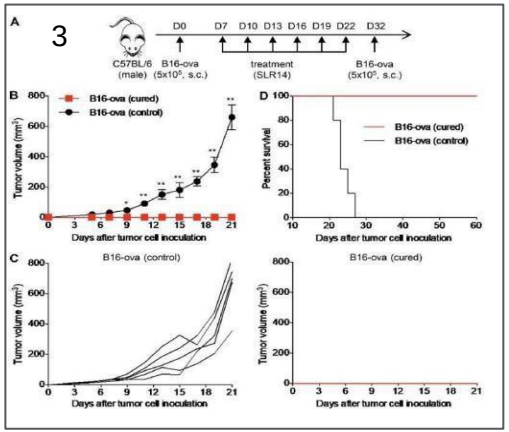


Figure 1. Combination treatment with SLR14 and anti-PD1 enhances antitumor effects compared to single-agent therapy. Tumor volume averages for each group of YMR1.7-bearing mice are shown.

Figure 2. Intratumoral (i.t.) SLR14 treatment induces a strong abscopal effect in a bilateral B16-ova:B16-ova tumor model.

Figure 3. Mice cured of B16-ova tumors after SLR14 treatment develop long-term immune memory.

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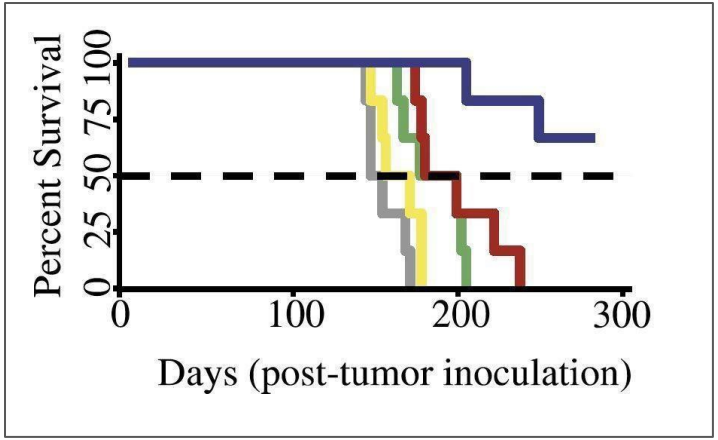
YV5840/6881: Treatment of Brain Tumors Using Enhanced Nanoparticles

Principal Investigator: Mark Saltzman, Ph.D.

Convection-enhanced Delivery of Drug-Loaded Nanoparticles to the Brain Tumors

- Biodegradable nanoparticles (NPs) have been optimized to penetrate through tumor tissue when delivered by convection-enhanced delivery (CED).
- Delivery of drug-loaded enhanced NPs by CED outperforms treatment with "standard" NPs or drug alone.
- Could also be used to deliver therapeutics to the brain for other indications besides oncology.
- **References:** Zhou et al., 2012 Cancer; 2013 PNAS; Ediriwickrema et et al., 2014 Biomaterials; Gaudin et al., 2016 Biomaterials; Saucier-Sawyer et al., 2016 J Control Release.
- **Patents Applications:** 20150118311; 20140371712



Kaplan-Meier survival curves for tumor-bearing rats: blue line, brain-penetrating paclitaxel NPs (median survival 46 d); red line, standard paclitaxel NPs (mediansurvival 38 d); green line, free paclitaxel (median survival 30 d); yellow line, blank NPs (median survival 31 d); grey line, no treatment (median survival 27 d)

YV5120: Universal Cancer Vaccine candidate

Principal Investigator: Madhav Dhodapkar, MD

Background:

- Traditional cancer vaccines are typically cancer-type specific, limiting their versatility and applicability.
- There is a need for universal cancer vaccines that can broadly target various cancer types.
- YV5120 serves as a novel "panvaccine" antigen that presents immunogenic epitopes for broad-based cancer immunotherapy.

Indications: Various cancer types, prevention of cancer-like side effects from stem cell therapies

Innovation & Asset:

- **Universal Target:** Applicable to numerous cancers, not limited to specific cancer types.
- **Immune Surveillance:** Recognized by the human immune system as a part of immune surveillance.
- **Embryonic Importance:** Targets proteins crucial for self-renewal and maintenance of pluripotency in embryonic stem cells.
- **Broad Efficacy:** Potential to elicit robust immune responses across various cancers.
- **Preventive Therapy:** YV5120-specific cellular therapy to prevent cancer-like side effects from stem cell therapies.

IP: US patent: 9,808,504

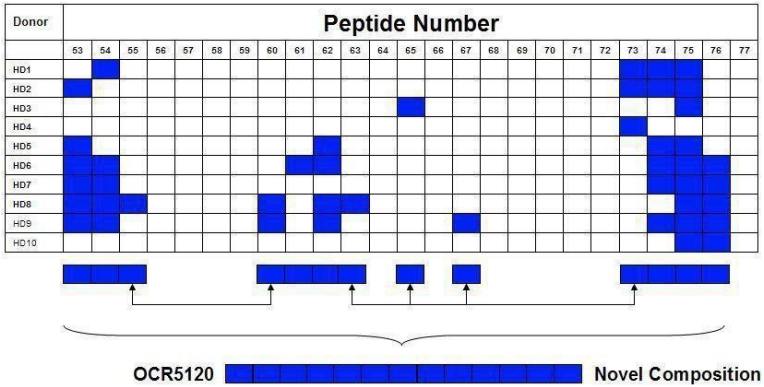


Figure 1: Map of OCR5120 immunogenic epitopes derived from human antigen isolated from patients (Short Blue) and vaccine candidate (Long Blue; OCR5120).

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YALE VENTURES

Neuroscience and Ophthalmology

YV9163: ULTRAMAC:ULTRA-THROUGHPUT MODULATION OF ABERRANT CONDENSATES

Principal Investigators: Christian Schlieker, PhD and Dylan Poch

Background:

- Aberrant biomolecular condensates contribute to over 600 human disorders, including dystonia, ALS, and frontotemporal degeneration (FTD).
- Current treatments fail to address the underlying molecular mechanisms of these diseases, limiting their effectiveness.
- UltraMAC offers a high-throughput, multiplexed screening approach to identify compounds that modulate toxic condensates across multiple diseases.

Indications: Dystonia, Amyotrophic Lateral Sclerosis (ALS), Frontotemporal degeneration (FTD), Huntington's Disease

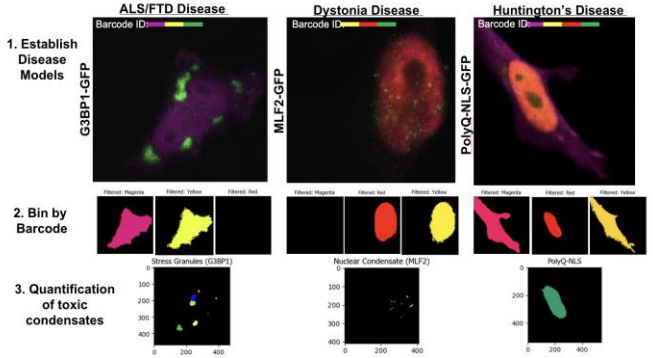
Innovation & Asset:

- **Multiplexed Screening:** Screens 30+ diseases simultaneously, maximizing efficiency in drug discovery.
- **Condensate Barcoding:** Unique fluorophore-tagged biomarkers allow rapid disease-specific quantification.
- **Polypharmacological Impact:** Increases likelihood of identifying drugs that target multiple disorders.
- **Scalable & High-Throughput:** Exceeds 100,000 compounds/day, improving drug screening efficiency.
- **Broad Applicability:** Potential extension beyond condensate diseases to other complex disorders.

IP: Patent application to be filed 2/13/2025

Learn More: Yale Life Sciences PitchFest

UltraMAC Multiplexed Screening of Aberrant Condensates



This figure demonstrates the UltraMAC platform for high-throughput modulation of disease-associated condensates. (1) Disease models are established using fluorescently labeled condensate biomarkers (e.g., G3BP1-GFP for ALS/FTD, MLF2-GFP for dystonia, and PolyQ-NLS-GFP for Huntington's disease). (2) Barcode filtering enables simultaneous tracking of multiple diseases by assigning distinct fluorophore combinations to each biomarker. (3) Quantification of toxic condensates is performed using computational analysis, allowing for precise measurement of condensate burden across disease models. This approach facilitates rapid identification of therapeutic compounds targeting multiple condensate-linked disorders.

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YALE VENTURES

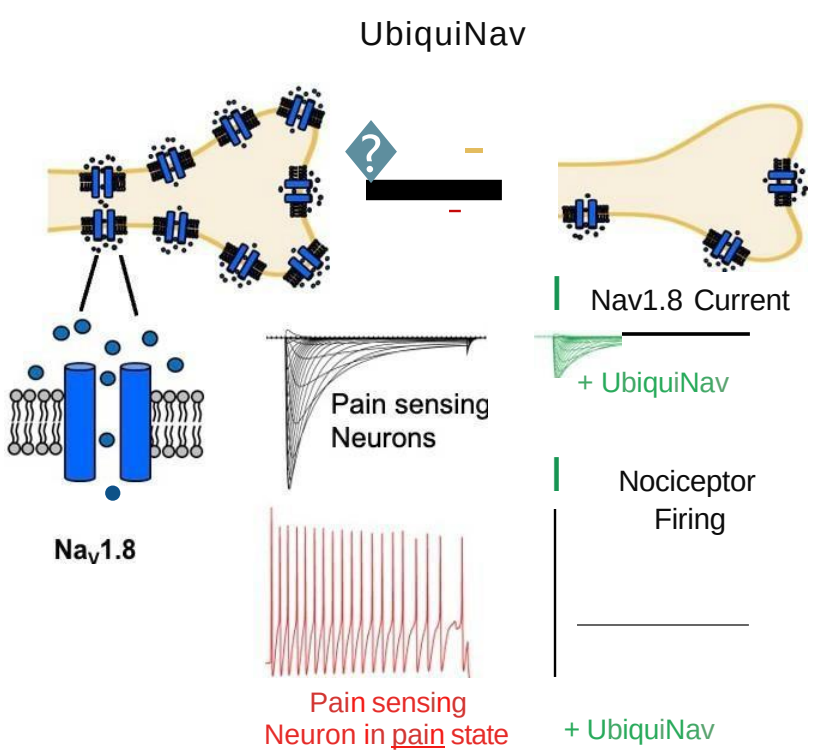
YV8723: UbiquiNav Targets the Voltage-Gated Channel Nav1.8 for Degradation

Background: The burden of chronic pain exceeds $600B in the U.S. alone, yet there are no FDA approved treatments for chronic pain. Navl.8 is a sodium channel expressed only in pain-sensing neurons, and an exceptionally well validated therapeutic target for the non-addictive relief of pain. However, all existing agents in the development pipeline are small molecules that directly bind to the channel. Trials of these agents have shown promise in acute pain indications, but with limited clinical efficacy.

Innovation: We engineered a gene therapeutic agent (UbiquiNav) that facilitates the degradation of Navl.8 channels in pain-sensing neurons. UbiquiNav is delivered via intrathecal injection of a viral vector. This approach has the potential to provide significant and durable pain relief in human patients.

Inventors: Sidharth Tyagi, MS, MPhil, Sulayman Dib-Hajj, PhD, Stephen Waxman, MD, PhD

IP Status: U.S. Provisional 63/580,094. Filed September 1, 2023.



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YV8507: Selective β1-AR antagonists to treat stress-related cognitive and/or emotional disorders

Principal Investigator: Amy Arnsten, PhD

Nonselective beta-adrenoceptor antagonist, propranolol, which blocks both β1-ARs and β2-ARs, is in widespread use for treating stress-related disorders such as PTSD.

Our new data show that **blocking both β1-ARs and β2-ARs would be suboptimal for treating stress disorders**, as they block both detrimental and beneficial receptors in dlPFC.

- selective β1-AR agonist xamoteral markedly reduces neuronal firing needed for working memory and higher cognition (Fig. a),
- selective β2-AR agonist procaterol enhances PFC neuronal firing (Fig. b).
- selective β1-AR antagonist, betaxolol, enhances PFC neuronal firing during higher cognition.
- The physiological data have been confirmed at the behavioral levels, where a pretreatment specifically selected to be low enough to have no effect on its own, prevented stress-induced with a low dose of the selective β1-AR antagonist, betaxolol (Beta, 0.001-0.1 mg/kg), cognitive deficits caused by FG7142

Our data suggest that a selective β1-AR antagonist should be more effective and would allow lower dosing to diminish side effects.

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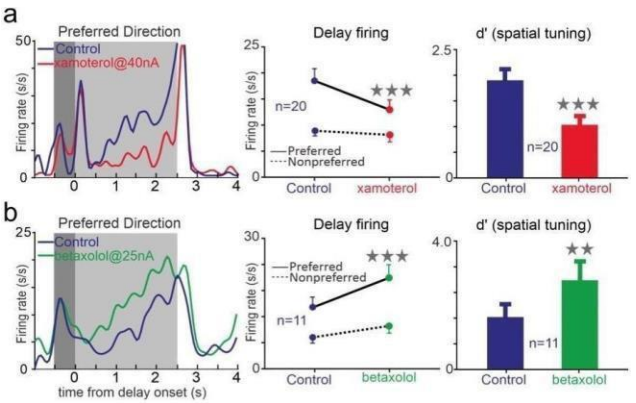
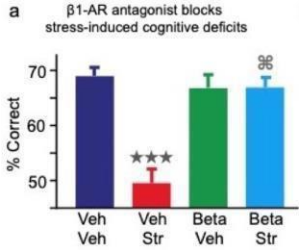
IP status: US Appl 63/424,811





Pretreatment with the selective β1-AR antagonist, betaxolol, prevented the cognitive deficits caused by FG7142 –induced stress in 6 macaques. Data represent mean+SEM percent correct on a working memory task.

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YV8224: Human cortical organoids with engineered microglia-like cells

Principal Investigator: In-Hyun Park, PhD

Background:

- Human cortical organoids (hCOs) are valuable for modeling 3D human brain tissue, but their lack of mesenchymal components, such as microglia, limits their potential.
- The incorporation of engineered microglia-like cells into hCOs enhances their utility for studying neurological diseases and developing new treatments.

Indications: Glioblastoma Multiforme (treatment); Neurodegenerative Disorders, Neurodevelopmental Disorders (model platform)

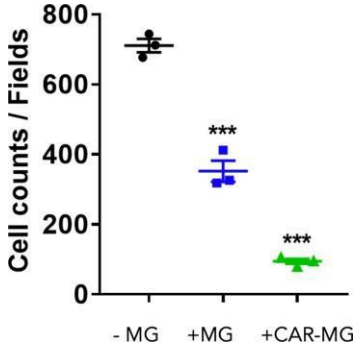
Innovation & Asset:

- **Advanced Model:** Novel platform developing microglia-containing hCOs using human embryonic stem cells.
- **Efficient Generation:** Tunable, efficient method of microglia generation, published in Nature.
- **Immunotherapy Potential:** Microglia may be modified with chimeric antigen receptors (CAR) for immunotherapy applications (A).
- **Enhanced Research:** Allows improved investigation of brain diseases like Alzheimer's (B), autism, and schizophrenia.
- **Broad Application:** Versatile platform for both disease modeling and therapeutic development

IP: US patent filed:18/715,012

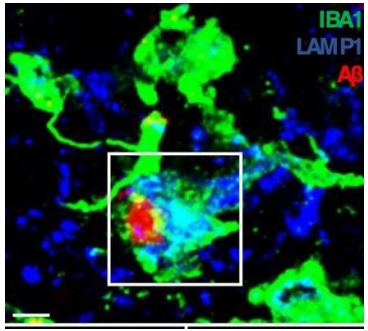
A

Chimeric antigen receptor microglia targeting EGFRvIII (+CAR-MG) demonstrate significantly improved tumor killing compared to unmodified microglia (+MG) and no microglia (-MG) using vitro models of EGFRvIII- positive glioblastoma multiforme.



B

Co-localization of IBA1 (a microglial protein), LAMP1 (lysosomal membrane protein), and Aβ (amyloid beta) in a microglia-containing human cortical organ model of Alzheimer's disease.



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YALE VENTURES

YV8216: Targeting Axonal Spheroids in Alzheimer's Disease

Principal Investigator: Jaime Grutzendler, MD

Background: Plaque-Associated Axonal Spheroids (PAAS)

- Accumulate near amyloid deposits in Alzheimer's Disease patients (**A**)
- Depend on expression of PLD3, a lysosomal protein (**A**)
- Disrupt electrical signal conduction in mouse models (**B**)

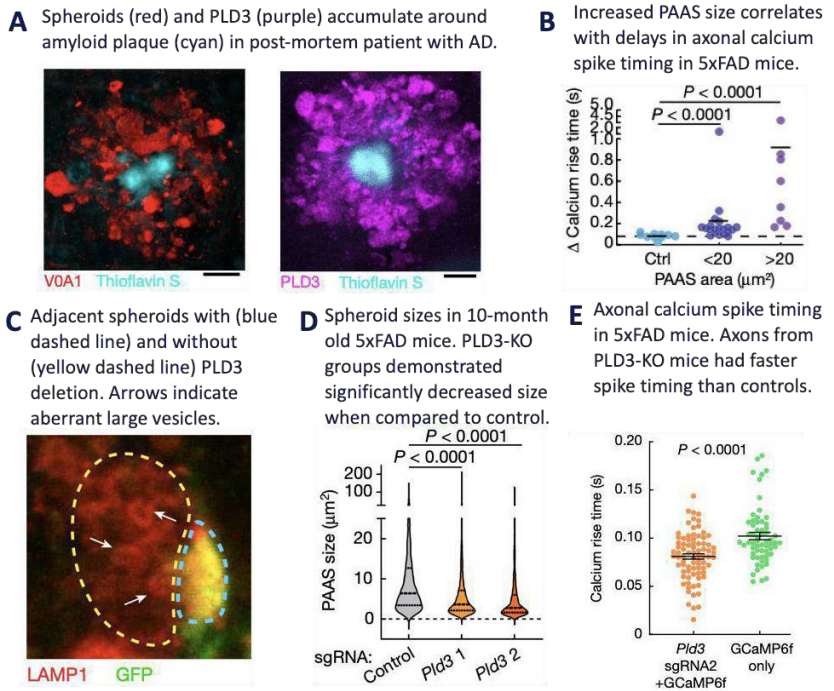
Indication: Alzheimer's Disease (primary), other neurodegenerative diseases (e.g. Parkinson's, TBI)

Innovation& Asset:

- PLD3 activity presents a novel target with in-vivo validation
- CRISPR-Cas9 KO of PLD3 results in decreased PAAS size (**C**, **D**) and ameliorates the signal conduction delays caused by a 5xFAD phenotype (**E**)
- Potential mechanisms for targeting PLD3 include antisense oligonucleotides, RNA interference, small molecules
- Additional unpublished targets and modalities (e.g., Mab Target)

PLD3 Publication: Nature 2022 Dec;612(7939):328-337

IP: US patent filed: 18/689,161



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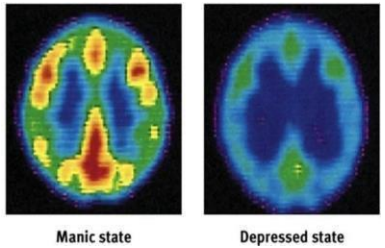
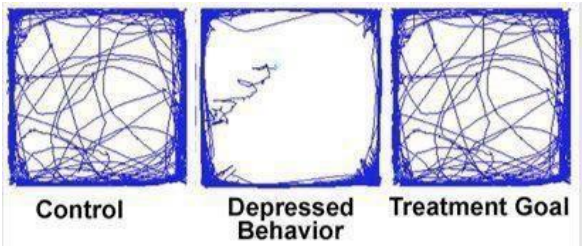
YV7709: Novel Druggable Target to Treat Bipolar Disease

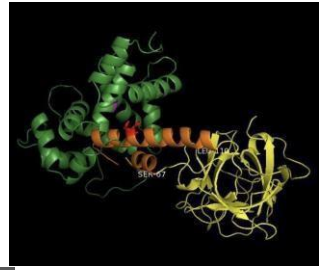
Principal Investigator: Barbara Ehrlich

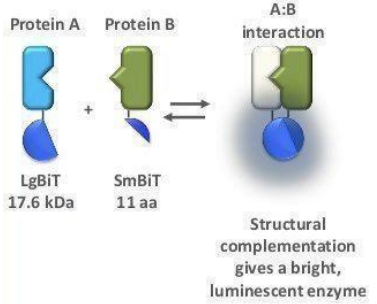
- 6 million adults in US have BP
  - severe mood swings
  - 1 in 5 commits suicide
- All available BP drugs: toxic, poor efficacy, or both
- Current trials lack novel compounds, mainly drug combinations
- YV5570 target levels affected in bipolar
  - Target structures + hits known
  - Screenable/Structure-based drug design
  - Animal models available for in vivo validation
- Critical protein-protein Interactions Identified
- Amenable to split renilla luminescence assay

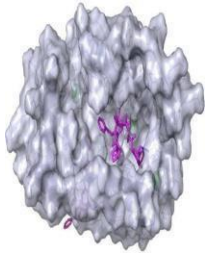


Baxter and Phelps, UCLA









IP: PCT/US2020/34539

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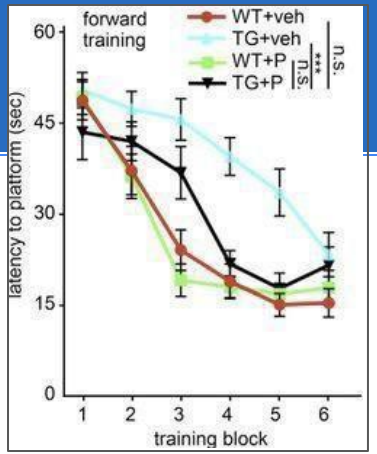
YALE VENTURES

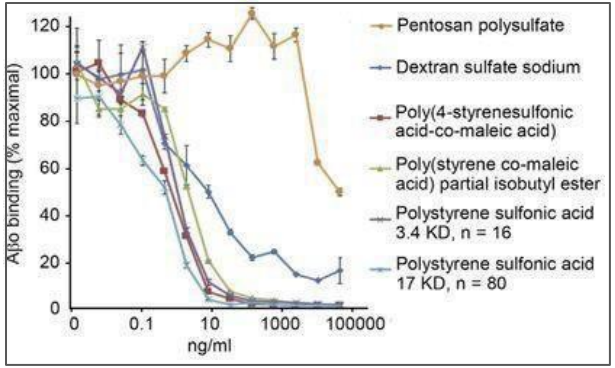
YV7470: Orally-available polymers to treat Alzheimer's Disease (AD)



Principal Investigator: Stephen M. Strittmatter, M.D., Ph.D.

Polar Anionic Polymers rescue AD by inhibiting Aβ/PrP

- Amyloid β-oligomers (Aβ) bind t neurons via Prion Protein (PrP), triggering neurotoxic cascade and Alzheimer's disease
- Polar anionic polymers bind to PrP with high affinity, inhibiting Aβ binding
- Oral delivery of PSCMA (Polymer 3) inhibits the Aβ/PrP interaction and rescues Alzheimer's disease-induced learning and memory deficits in mice
- **IP:** US 2021/0268016 A1 patent filed 1/6/2021



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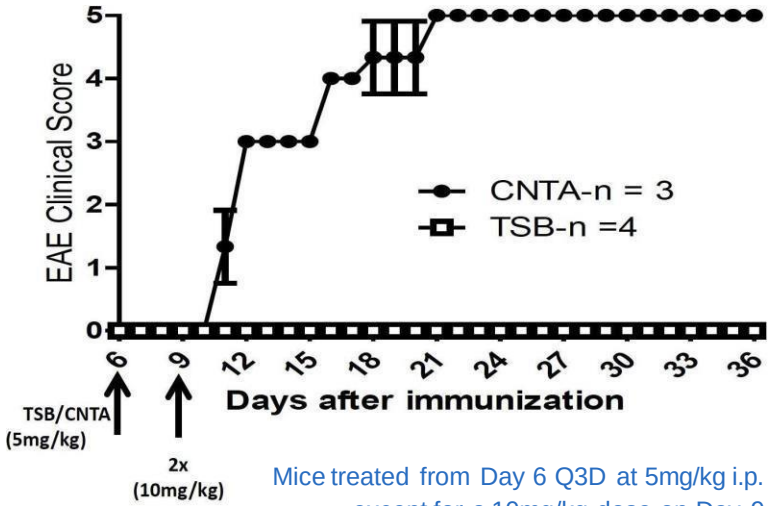
YALE VENTURES

YV7398: Reduction of IL-17A with an Inhibitor of miR466l-3p Binding to IL-17A mRNA

Principal Investigator: Jeffrey Bender

- The microRNA miR466l-3p stabilizes IL-17A mRNA thereby increasing IL-17A levels.
- IL-17A plays a pathogenic role in multiple inflammatory diseases (e.g., MS, IBD, Psoriasis).
- A nucleotide has been developed that selectively blocks this miR466l-3P site on the IL-17A mRNA, and reduces IL-17A levels.
- In vivo proof of concept of this therapeutic approach has been demonstrated in two mouse models of MS.
- A provisional patent application has been filed.

miR466l-3p/IL-17A Target-Site Blocker (TSB) in a progressive EAE mouse model of MS. (2D2 Transgenic)



Mice treated from Day 6 Q3D at 5mg/kg i.p. except for a 10mg/kg dose on Day 9.

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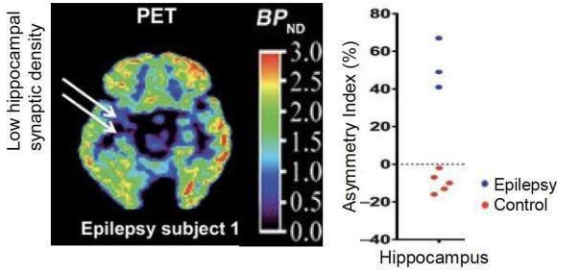
YV7160: Radiopharmaceuticals for Synaptic Imaging

Principal Investigator: Jason Cai, PhD

Fluorine-18 labeled radiopharmaceuticals for SV2A imaging and as biomarkers of synaptic density

- Many neurological and psychiatric diseases, such as Alzheimer's and Epilepsy, are characterized by misfiring synapses. Currently, there is no way to visualize healthy or aberrant neuronal connections in the living human brain.
- SV2A radioligands combined with positron emissiontomography (PET) can be used to noninvasively quantify synaptic density in the living human brain.
- Fluorine-18 labeled SV2A radioligands have a longer half-life (110 min) making them suitablefor commercialization and clinical applications.
- This promising method enables routine brain monitoringin patients with neurological diseases, where synaptic loss or dynamic changes in density could provide clues to prognosis.
- **Reference:** Finnema et al. (2016) Science
- **IP status:** EP and US Patents issued(US11,518,754)

PET evaluation with SV2A radioligandreveals unilateral sclerosis in epilepsy patients.



(Left)Thewhitearrowsindicate loss of SV2A radioligand binding in the mesialtemporal lobe. (Right)Asymmetry indices betweenleft andright hemispheres for healthy control subjectsandbetween ipsilateral and contralateral hemispheres for epilepsypatients. Data are individual subjects

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YALE VENTURES

YV7050: Multimodal Brain Monitoring

Principal Investigator: Hitten Zaveri

Neuroprobe sensor

- NeuroProbe is a brain implantable device for multimodal brain monitoring in the Neuro-ICU.
- Makes early detection of secondary brain injury post TBI possible, which, if detected early, may be reversible.
- The integration of sensors on a single probe co-locates data acquisition, a dramatic improvement for research, beyond patient benefit.
- Portable multimodal interface device NeuroLink stores and relays the digital data to standard clinical monitors or a portable monitor.
- Placement possible at bedside or at a military field facility.

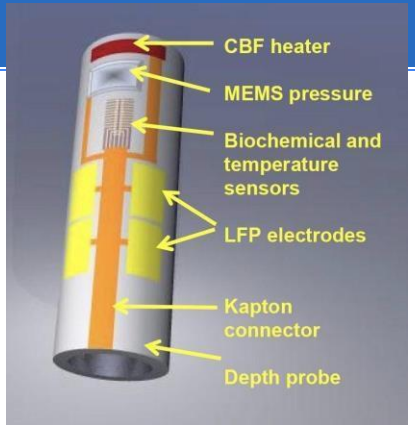

Fig 1. Intracranial pressure (icP), intracranial EEG (icEEG), intracranial temperature (icT), brain tissue oxygen (PBTO2) and cerebral blood flow (CBF)

Approach	Number of Probes	Reliability	Ease of Use	Cost
Current	X	✓	X	X
NeuroProbe	✓	✓	✓	✓

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YALE VENTURES

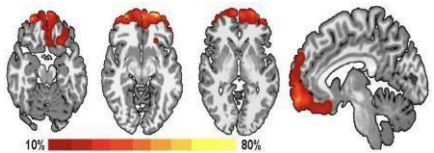
YV6980: Neurofeedback Therapy for Treatment of OCD

Principal Investigator: Chris Pittenger, MD/PhD

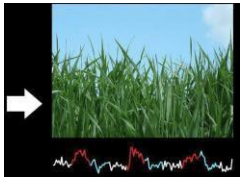
Functional near-infrared spectroscopy (fNIRS)-driven feedback for psychiatric symptoms

- Many neuropsychiatric conditions, including OCD, are characterized by regionally abnormal brain activity.
- Only~60% of patients respond to standard OCD interventions and these options affect the entire brain causing undesirable off-target effects.
- Studies have revealed hyperactivity of a specific brain region, the OFC, in patients with OCD making it an attractive therapeutic target.
- NIRS-driven neurofeedback therapy is optimized for such conditions: it is more affordable than fMRI, portable, non-invasive and targeted to control activity of affected neural areas.
- In NIRS, the signal reflects the metabolic activity of a defined brain area and patients can use the visual readout of this activity to learn via trial-and-error to control its activity.
- This therapy can lead to altered functional connectivity within the targeted circuitry that persists even in the absence of ongoing efforts at control

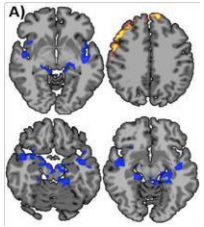
Stimuli-responsive regions of the OFC are identified in OFC patients during Neurofeedback protocol



Display observed by patients



fNIRS alterations of neural activity persist: reductions in anxiety-linked areas (blue) and increases in areas associated with cognitive control (yellow) are observed



IP Status: Pending

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YALE VENTURES

YV6953: Antigenic Peptides Help Antibody Access to the Brain

Principal Investigator: Akiko Iwasaki, PhD

Background:

- Antigen-specific CD4+ T cells recognize cognate antigens presented by perivascular APCs, secreting IFN-γ, which reduces tight junctions between endothelial cells (ECs).
- This process allows circulating antibodies to cross the blood-brain barrier (BBB) and access the brain parenchyma.

Indications: Neurotropic viruses, brain cancers

Innovation & Asset:

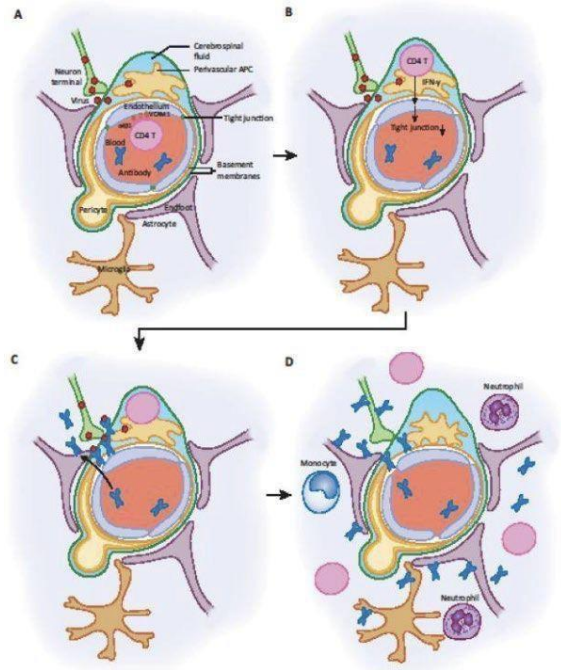
- **CD4+ T cells:** Enables antibody access to the brain.
- **Established foundations:** Basis for future therapeutic.
- **Therapeutic targeting:** Potential for treating neurotropic viruses and brain cancers.

Publications:

- Iwasaki A. Immune Regulation of Antibody Access to Neuronal Tissues. Trends Mol Med. 2017;23(3):227-245.
- Iijima N, Iwasaki A. Access of protective antiviral antibody to neuronal tissues requires CD4 T-cell help. Nature. 2016;533(7604):552-6.

IP: Multiple national patents filed; US patent: 11,147,862

Step-by-step Progression of Immune Response to Viral Infection at the Neuron Terminal



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YALE VENTURES

YV6282: Therapeutic Inhibition of Phospho- Tau in the Primate Prefrontal Cortex

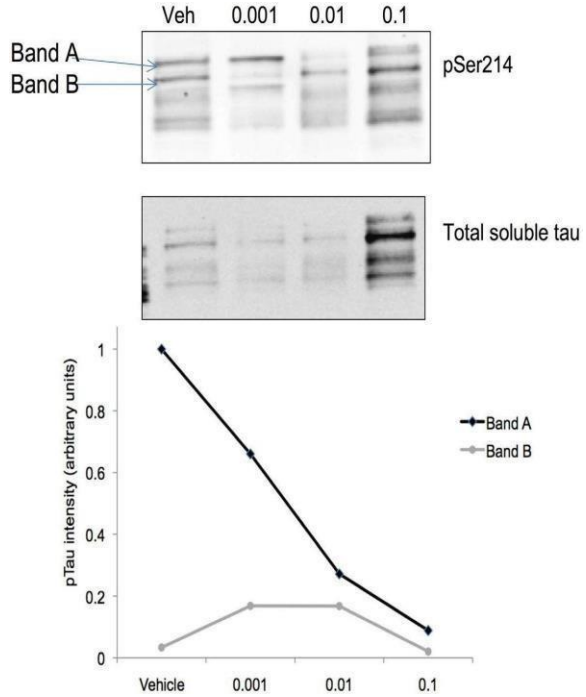
Principal Investigator: Amy Arnsten, PhD

Age-related increase in phosphorylation of tau and its aggregation at the dendritic spines of the cortical pyramidal neurons results in formation of neurofibrillary tangles (NFT), eventually leading to neurodegeneration in the PFC

In humans, tau phosphorylation begins relatively early in the aging process, suggesting that interventions to prevent PFC neurodegeneration need to be initiated at younger ages.

In the NHP, we show chronic treatment (6 months, daily) with low doses of an alpha-2A adrenergic receptor (α_{2A} AR) agonist reduces and/or reverses the high level of p-tau in the PFC, thus reducing the risk of neurodegeneration. Such α_{2A} AR agonist-induced decrease of p-tau enhances cognition in NHP (figure)

We propose chronic use of low doses of α_{2A} AR agonists for prevention or reduction of the age-related cognitive disorders such as Alzheimer's Disease at early stages.



IP status: US 10022341 B2 issued 7/17/2018

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YALE VENTURES

YV5007: A Novel Approach to Treating Alzheimer's Disease

Principal Investigator: Richard Flavell, PhD, FRS

Background:

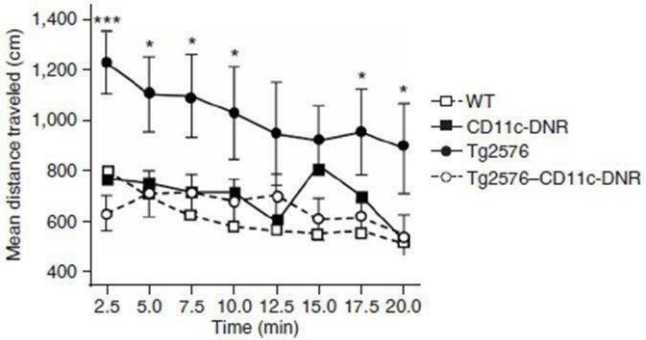
- Alzheimer's disease impacts millions globally, characterized by β-amyloid plaque accumulation.
- Current treatments offer limited efficacy, often targeting neural pathways with marginal success.
- This new technology blocks TGF-β signaling in peripheral macrophages, effectively clearing β-amyloid plaques.

Indications: Alzheimer's disease

Innovation & Asset:

- **Peripheral Action:** Targets peripheral TGF-β signaling.
- **Blood-Brain Barrier:** No need to cross the blood-brain barrier.
- **Plaque Reduction:** Effective in clearing β-amyloid plaques.
- **Novel Mechanism:** Utilizes a unique pathway.
- **Therapeutic Potential:** Offers significant therapeutic intervention advancements.

IP: Multiple national patents issued: 2299812; issued US patent: 9,095,126



Expression of a CD11c promoter–driven dominantnegative TGF-β receptor type II in an Alzheimer's disease mouse model (Tg2576–CD11c-DNR) improved Alzheimer's-like behavioral impairment such as hyperactivity.

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YV4677: Antibodies Against Prion Proteins for Treatment of Alzheimer's Disease

Principal Investigator: Stephen M. Strittmatter, M.D., Ph.D.

- **Background:** Cellular prion protein PrPC acts as a high affinity receptor for Aβ-oligomers and is required for Aβ-oligomer-induced synaptic dysfunction in vitro and in vivo. Signal transduction downstream of Aβo/PrPC involves mGluR5, Fyn and Pyk2.
- In an AD Tg mouse model an infusion of the anti-PrPC mAb produces a significantbehavioral rescue in the setting of advanced disease, even with a relatively short treatment regiment (Fig.1).
- **Indications:** Alzheimer's Disease; prion-related diseases (CJD, etc).
- **References:** Heiss et al. (2016) Cereb Cortex; Salazar et al. (2017) Biochem Biophys Res Comm.
- **IP status:** Issued patent US 9217036

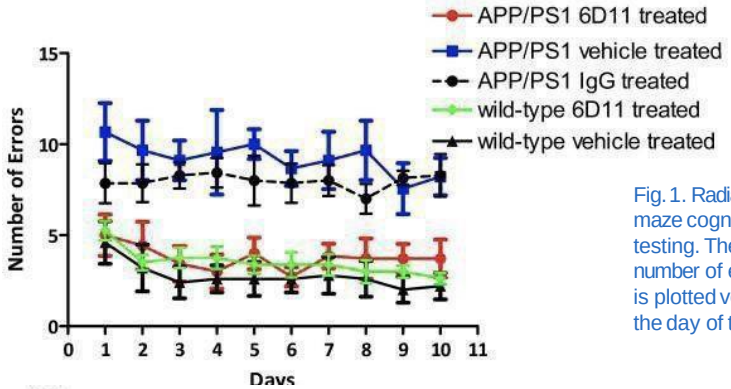

Fig. 1. Radial arm maze cognitive testing. The number of errors is plotted versus the day of testing.

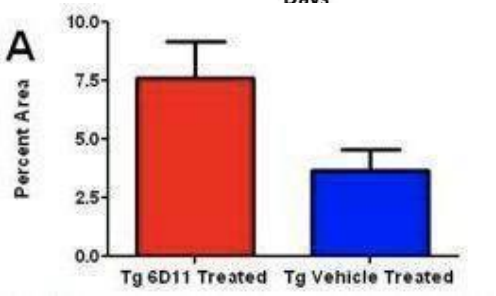

Fig. 2. Synaptophysin immunoreactive presynaptic terminals in the molecular layer of the dentate gyrus of the hippocampus.

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YALE VENTURES

Therapeutics:

Cardiac, Pulmonary, Hepatic, Metabolic and Fibrotic Disease

YV9197 : FERROPTOSIS SUPPRESSERS LIPOSOME-ENCAPSULATED AKR1

Principal Investigator: Dianqing (Dan) Wu, PhD

Background:

- Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) have high mortality rates, affecting millions globally.
- Current treatment focuses on ventilation support; pharmacological interventions are ineffective due to unresolved causes of alveolar damage and cell interplay.
- New technology uses extracellular vesicle-associated AKR1B8 to protect alveolar cells from inflammation-induced ferroptosis.

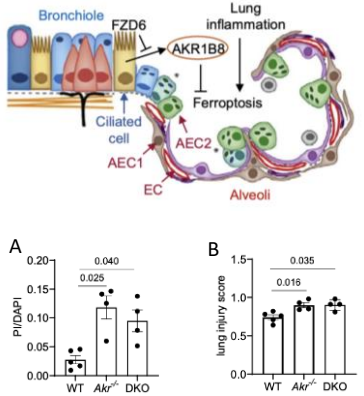
Indications: Acute Lung Injury, Acute Respiratory Distress Syndrome, COVID-19 related lung injury, SARS, MERS.

Innovation & Asset:

- **Non-Cell Autonomous:** Utilizes extracellular vesicles for AKR1B8 delivery.
- **Ferroptosis Suppression:** Protects alveolar cells from iron-dependent lipid peroxidation.
- **Inflammation Reduction:** Reduces alveolar and lung injury during inflammation.
- **Broad Applicability:** Effective against bacterial, viral infections causing ALI/ARDS.
- **Enhanced Survival:** Potentially decreases mortality rates in severe respiratory conditions.

IP: Patent application filed.

Extracellular vesicle AKR1B8 from ciliated epithelial cells suppresses ferroptosis of alveolar cells during lung inflammation



AKR1B8-deficiency exacerbates alveolar cell death and lung injury Phenotypes. (A) Quantification of Bronchoalveolar Lavage (BAL) Fluid Isolated from Wild Type (WT), Akr1b8-/-, and Akr1b8-/-Fzd6foxj1 (DKO) mice, post-LPS treatment. Increased levels of FITC-dextran indicate a higher degree of lung permeability and injury in Akr1b8-/- and DKO mice compared to WT, demonstrating the protective role of AKR1B8 against lung injury. **(B)** Lung injury scores derived from histological analyses of lung sections from WT, Akr1b8-/-, and DKO mice, following LPS treatment. Higher injury scores in Akr1b8-/- and DKO mice compared to WT further support the protective effect of AKR1B8.

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YALE VENTURES

YV8905: ENPP1 LONG-ACTING BIOLOGICS FOR CHILDHOOD AND ADULT OBESITY AND ASSOCIATED WITH THE ENPP1 K121Q SNP

Principal Investigator: Demetrios Braddock, MD, PhD

Background:

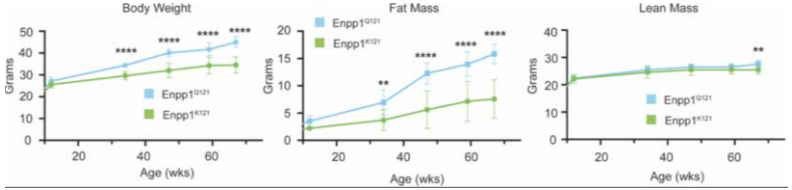
- Genetic obesity associated with the ENPP1Q121 SNP, present in 66 million U.S. adults and children.
- Current obesity interventions fail to address genetic risks and metabolic complications.
- This technology targets ENPP1Q121, addressing obesity, insulin resistance, and metabolic syndrome.

Innovation & Asset:

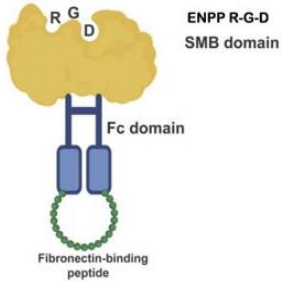
- **Predictive Model:** Mouse model replicates ENPP1Q121-driven obesity and metabolic traits.
- **Mechanistic Insights:** Identifies ENPP1Q121's role in preadipocyte differentiation and lifelong obesity risk.
- **Therapeutic Screening:** In vitro assays for validating biologics targeting ENPP1Q121.
- **Lead Asset:** Provisional patents filed for novel biologics reducing ENPP1Q121-mediated adipogenesis.
- **Comprehensive Approach:** Combines genetic insights with therapeutic development to tackle obesity at its root.

IP: Patent application filed.

Learn More: Yale Life Sciences PitchFest



Longitudinal body composition analysis of ENPP1Q121 (light blue) and ENPP1K121 (green) mice from 10 to 70 weeks. **(Left)** ENPP1Q121 mice exhibit greater body weight gain than ENPP1K121 mice. **(Middle)** Fat mass is significantly higher in ENPP1Q121 mice, reflecting increased adiposity seen in human Q121 variant carriers. **(Right)** Lean mass differences are minimal, with a slight but significant increase in ENPP1Q121 mice at the final time point (p<0.01, **** p<0.0001).



This schematic illustrates the design of a lead biologic targeting obesity, identified through in vitro assays. The construct features the ENPP RGD-containing SMB domain fused to an Fc domain for stability and circulation, with a fibronectin-binding peptide for targeted activity. This biologic leverages ENPP-based mechanisms for potential obesity treatment.

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YALE VENTURES

YV8441: Targeting uORFs in PKD

Principal Investigator: Whitney Besse, MD

Background:

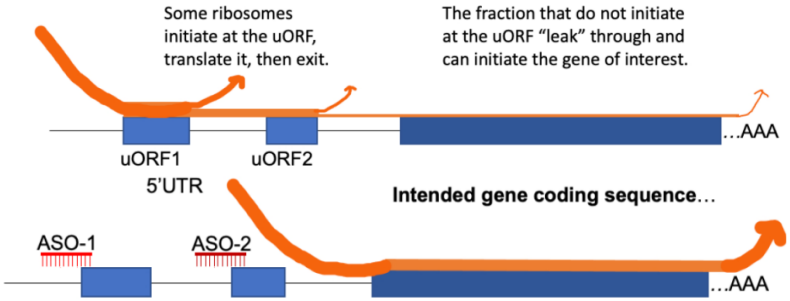
- Autosomal dominant polycystic kidney disease (ADPKD) affects over 12 million individuals worldwide, leading to kidney failure
- Polycystic liver disease (PCLD), often occurring with ADPKD, causes severe liver enlargement and related symptoms in 20% of patients.
- Current treatments for ADPKD and PCLD are limited, with significant side effects and a lack of FDA-approved therapies for liver cysts.
- The new technology specifically targets upstream open reading frames (uORFs) in the PKD1 gene, enhancing PC1 protein production.

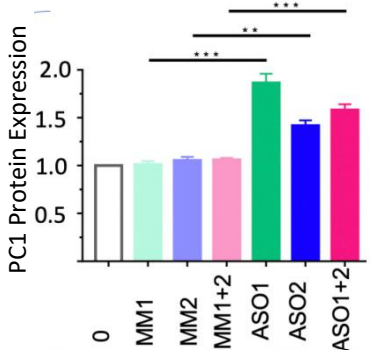
Indications: ADPKD, PCLD

Innovation & Asset:

- **Gene Targeting:** Suppresses translation of PKD1 uORFs to increase functional polycystin-1 (PC1) levels
- **High Specificity:** Utilizes antisense oligonucleotides (ASOs) for precise targeting of unique uORF sequences
- **Enhanced Translation:** Demonstrated 2-fold increase in PKD1 translation efficiency, preventing cyst formation
- **Comprehensive Application:** Effective for patients with both ADPKD and isolated PCLD, offering a long-term therapeutic solution

IP: PCT/US2023/023414 filed May 24, 2023





ASO treatment in culture media of human epithelial cells significantly increases the protein expression of PC1 without effecting mRNA expression

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YALE VENTURES

YV8436: TET3 Inhibition for Treatment of NASH, Fibrosis, Anorexia, and Cancer-Induced Depression

Principal Investigator: Yingqun Huang, MD, PhD

Background:

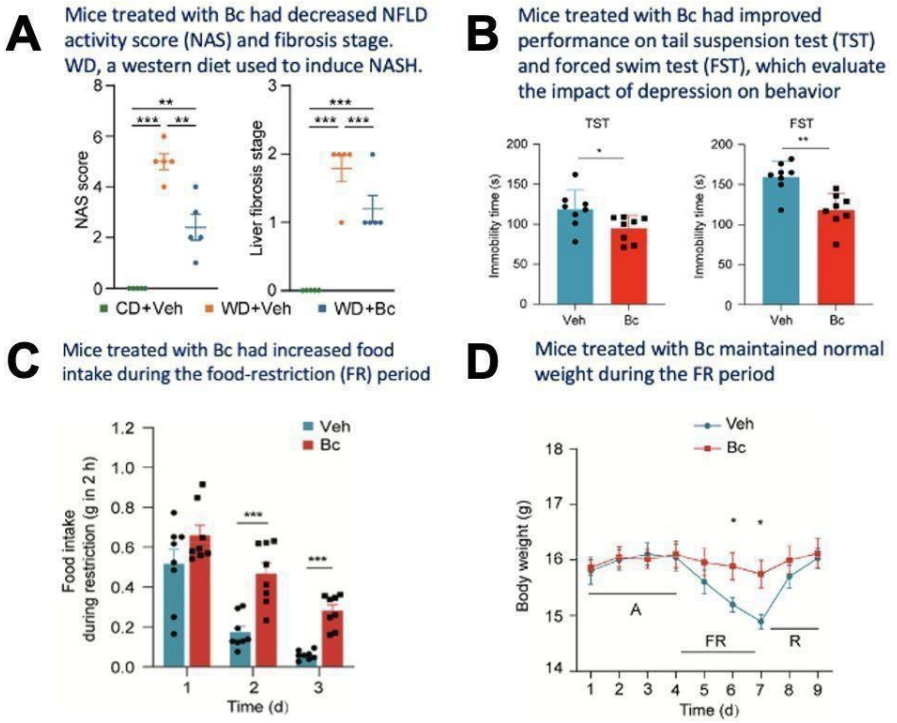
- TET3 knockdown in macrophages ameliorates nonalcoholic steatohepatitis (NASH), liver fibrosis, and endometriosis
- TET3 knockdown in AgRP neurons leads to increased appetite and anti-stress effects (Xie et al, *JCI*, 2022; Lv et al, PNAS, 2023)

Indications: NASH, fibrosis, anorexia, depression,

endometriosis Innovation & Asset:

- **Effective Inhibitor:** Small-molecule Bobcat339 specifically degrades TET3 protein.
- **Multifaceted Benefits:** Decreases NASH/fibrosis (A) and depressive behaviors (B).
- **Appetite Improvement:** Enhances appetite (C) and body weight (D) in anorexia models.
- **Safe and Tolerable:** Demonstrates no toxicity and is well-tolerated.

IP: PCT/US2023/75802



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YALE VENTURES

YV 8381: GLIS2 as a Target for Autosomal Dominant Polycystic Kidney Disease

Principal Investigator: Stefan Somlo, MD

Background:

- Polycystic Kidney Disease (PKD) affects ~12.5 million individuals WW and is characterized by slow cyst growth in the kidneys, leading to renal failure.
- Current therapies, such as tolvaptan, have limited efficacy and significant side effects.
- Somlo Lab at Yale identified GLIS2, a transcription factor, as a promising target for halting cyst progression, offering a more targeted therapeutic approach for PKD.

Indications: PKD, kidney cystic diseases, chronic kidney disease (CKD), ADPKD

Innovation & Asset:

- **Novel Target:** GLIS2 identified as a transcriptional regulator linked to PKD progression, providing a tractable target for therapy.
- **Therapeutic Delivery:** Targeting Glis2 with antisense oligonucleotides (ASOs) results in reduced disease progression of animal models of ADPKD.
- **Role of Glis2 is validated In vivo:** significant reduction in cyst growth, kidney enlargement, and fibrosis.Targets early-stage cyst formation and prevents disease progression more effectively than current treatments.
- **High Clinical Potential:** Applicable to early and late-stage PKD patients, offering a breakthrough alternative for managing kidney cystic diseases.

Publication: *Nat Commun. 2024 May 1;15(1):3698*

IP Status: US and EU Patents Filed on 04/2024

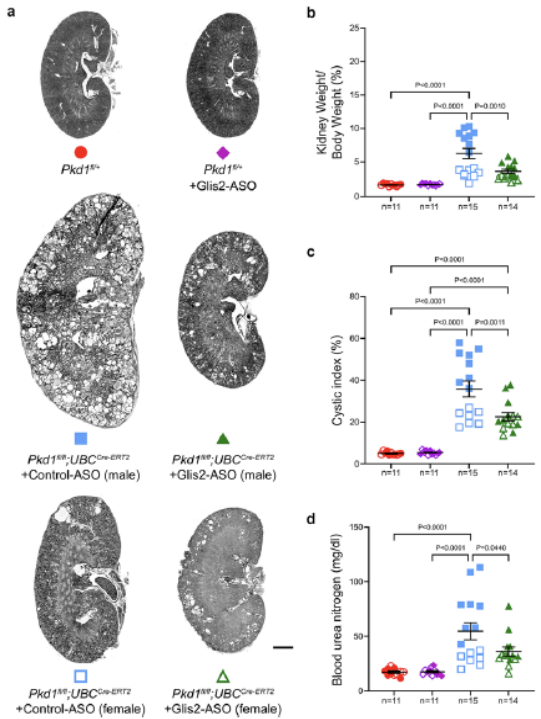

Figure: Glis2 antisense oligonucleotide (ASO) reduces kidney cyst growth in an adult onset ADPKD model

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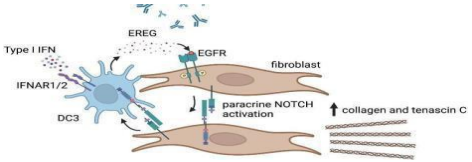
YALE VENTURES

YV8349: Epiregulin Inhibition to Treat Skin and Lung Fibrosis

Principal Investigator: Ian Odell, MD, PhD, FAAD and Richard Flavell, PhD, FRS

Background:

- Epiregulin (Ereg) activates EGFR, creating a pro-fibrotic feedback loop between DC3 dendritic cells and fibroblasts

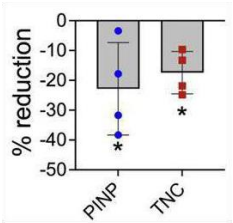


Innovation & Asset:

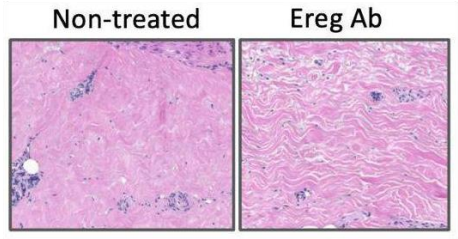
- **Monoclonal Ereg Ab:** Monoclonal human epiregulin-neutralizing antibody.
- **Skin Biopsies Efficacy:** Ex vivo skin biopsies of patients with systemic sclerosis (**A**, **B**) and Graft vs Host Disease(**C**, **D**) demonstrate decreased pro-fibrotic protein expression and decreased fibrosis on Histology.
- **Lung Biopsies Efficacy:** Showed reduced pro-fibrotic protein expression in lung biopsies from idiopathic pulmonary fibrosis patients.
- **Precision Treatment:** Offers higher precision over existing EGFR and cytokine-targeting therapies.
- Full publication in Science Immunology

IP: PCT/US2023/14512

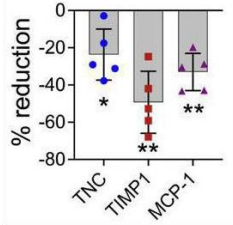
A In skin from patients with systemic sclerosis, Ereg Ab treatment reduces levels of fibrosis markers Pro-COL1A1 N-terminal peptide (PINP) & Tenascin C (TNC)



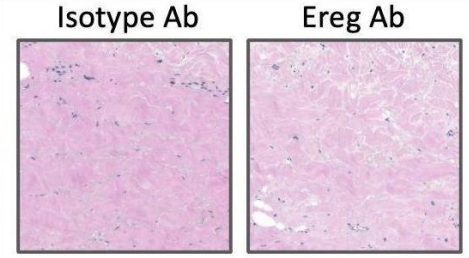
B In human scleroderma skin, Ereg Ab treatment reduces levels of fibrosis (note decreased density of pink fibers with treatment)



C In skin from patients with GvHD, Ereg Ab treatment reduces levels of fibrosis markers Tenascin C (TNC), Tissue Inhibitor of Matrix Metalloproteinase 1 (TIMP-1), and Monocyte Chemoattractant Protein-1 (MCP-1)



D In human GvHD skin, Ereg Ab treatment reduces levels of fibrosis (note decreased density of pink fibers with treatment)



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YALE VENTURES

YV8151: Novel Therapeutic Approach for Pulmonary Fibrosis

Principal Investigator: Farida Ahangari, MD

Background:

- Idiopathic pulmonary fibrosis is a deadly, progressive lung disease with limited treatment options
- miR-33 is a microRNA that regulates macrophage metabolism

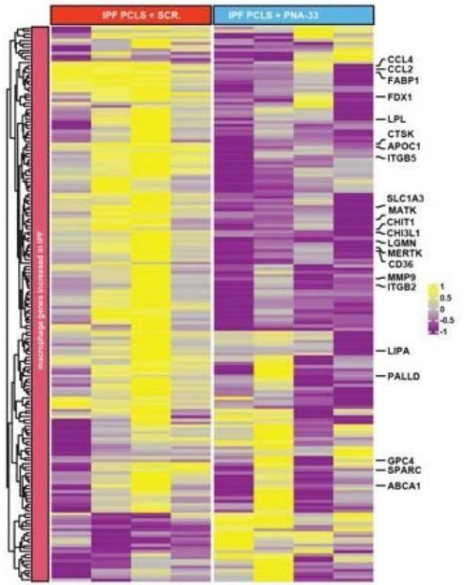
•**Indications:** Idiopathic Pulmonary Fibrosis (IPF)

Innovation & Asset: Peptide-nucleic acid ("PNA-33") that inhibits miR-33 expression

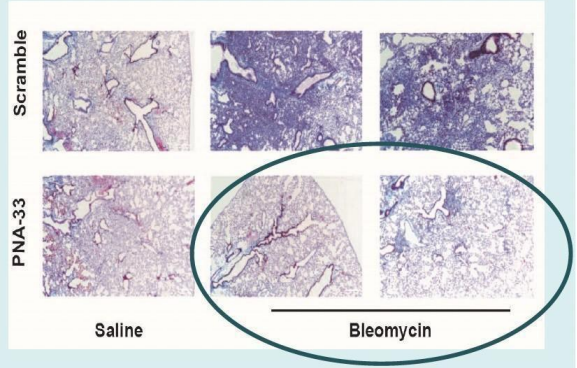
- Decreases lung fibrosis in vivo (mouse models) and ex vivo (samples from mouse and human)
- Improves lung fibrosis on histology in mouse models
- Stable, safe, easily-modifiable compound

•**IP:** US Patent Application 17/663,378

Right: Macrophages isolated from human IPF patient samples demonstrate a decreased fibrotic expression profile after treatment with PNA-33 (right, blue lanes) when compared to the scrambled sequence (left, red lanes).



Below: In-vivo mouse models of IPF using bleomycin demonstrate decreased fibrosis after intranasal treatment with PNA-33 compared to the scrambled sequence.



Contact: Lolahon Kadiri, PhD / lolahon.kadiri@yale.edu

YV7672: L-BAIBA as a novel therapeutic for phosphate disorders

Principal Investigator: Clemens Bergwitz, M.D.

Background:

- ~500,000 patients in the US have hyperphosphatemia, primarily those with chronic kidney disease, which leads to comorbidities
- Current medications to treat hyperphosphatemia often cause stomach cramping and diarrhea, leading to discontinuation

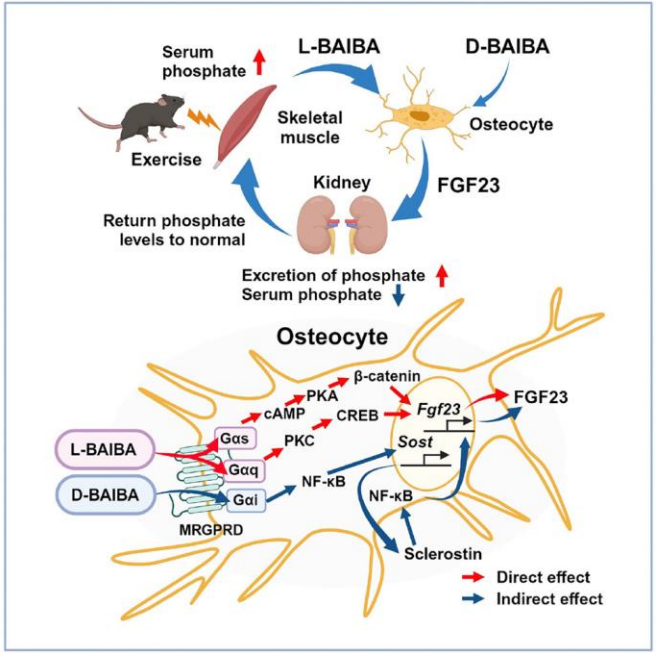
Indications: Phosphate disorders; nephropathies (CKD, IgAN, etc.)

Innovation & Asset:

- Myokine (S)-3-aminoisobutyric acid (L-BAIBA) was found to be a novel regulator of phosphate (P_i) excretion from the bone through FGF23
- Therapeutic administration of L-BAIBA can help stimulate the reduction of blood P_i while maintaining muscle and bone strength to treat hyperphosphatemia

Publication: Sakamoto, et. al., *Cell Reports*, 2024. (PMID: 38935499)

IP: US 17/761,020



YV7385: Disrupting Syndecan-2 for Treating Vascular Pathology and Leakage

PARTNERED

Principal Investigator: Michael Simons, M.D.

Background:

- Syndecans, particularly Syndecan-2 (Sdc2), facilitate growth factor signaling in endothelial cells.
- VEGF plays a crucial role in regulating vascular permeability during inflammation and tissue injury.
- Deletion of Sdc2 leads to significant vascular defects and impaired VEGFA165 signaling, traced to a specific sequence in Sdc2.

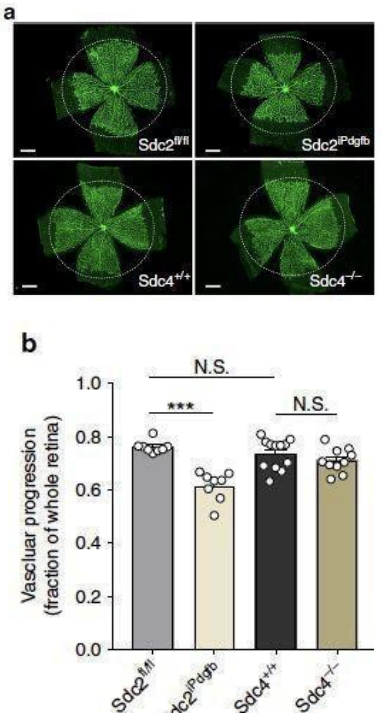
Indications: Cardiovascular diseases, Neurologic diseases, Retinopathy

Innovation & Asset:

- **Disruption Technology:** Syndecan-2 disrupting agent.
- **Vascular Protection:** Potential treatment for cardiovascular and neurologic diseases.
- **Eye Health:** Therapeutic application in retinopathy.
- **Mechanism:** Targets a specific 59 a.a. sequence in Syndecan-2.
- **Proven Efficacy:** Demonstrated significant impact on VEGFA-induced vascular permeability.

References: Corti et al, Nature Comm 2019

IP: PCT/US2019/34644



Sdc2, but not Sdc4, EC deletion leads to impaired angiogenesis. a. Retinas from P6 pups for each genotype (500 µm scale bars). b Quantification of vascular progression expressed as ratio between length of vascular front and retina edge (n = 8–12 retinas from 4 to 6 mice, each dot corresponds to a different retina).

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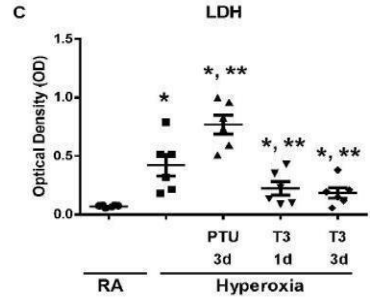
YV7357: Methods of Treatingor Preventing Acute Respiratory Distress Syndrome

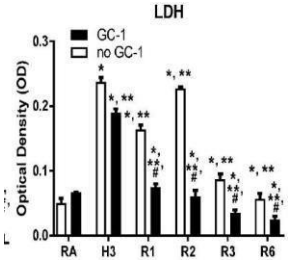
PARTNERED

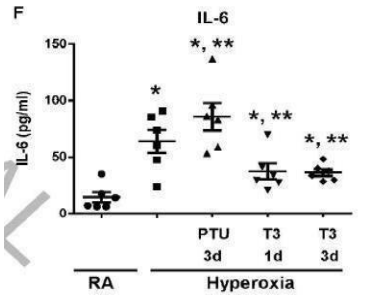
Principal Investigators: Naftali Kaminski, MD; Patty Lee, MD

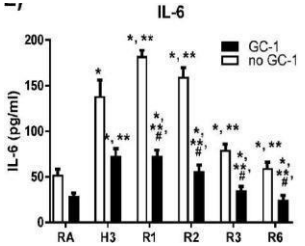
Inhaled Sobetirome as a novel therapeutic agent in ARDS

- Acute Lung Injury/Acute Respiratory Distress Syndrome (ALI/ARDS) is a major cause of respiratory failure.
- 200,000 adults and 15,000 children in US are affected with ARDS, with a mortality rate of ~40%.
- Treatment options are limited to mechanical ventilation. No FDA approved drugs on the market yet.
- Thyroid hormone (TH) and the thyroid receptor agonist Sobetriome (GC-1) attenuate hyperoxia induced ALI in WT mice.
- **IP Status:** U.S. provisional patent application 62/641,643









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YALE VENTURES

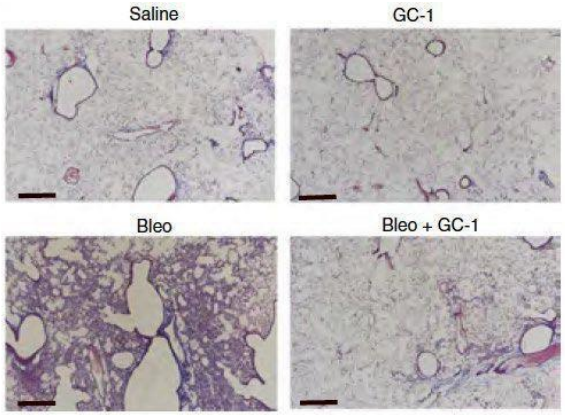
YV7270: Thyromimetics for fibrotic lung diseases

PARTNERED

Principal Investigators: Naftali Kaminski, M.D.

Sobetirome as a novel therapeutic agent in fibrotic lung diseases

- Idiopathic pulmonary fibrosis (IPF) is a lethal progressive chronic lung disease of unknown origin, with median survival of 3 years. 6M worldwide and 190,000 in USA are affected with IPF.
- Market expected to reach $3.2 billion by 2025.
- 2 FDA approved drugs show 40% reduction in disease progression, but no impact on QOL or survival. Side effects are significant (gastrointestinal, liver and photosensitivity), leading to poor patient compliance.
- Sobetirome (GC-1) is well characterized thyromimetic drug. in vivo animal proof of concept in IPF shows significant resolution of fibrosis
- **IP Status:** PCT/US 15/317,276



Yu et al, NatureMedicine 2018

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YV7100: NASH - Allosteric Targeting of Phosphatase

Principal Investigator: Anton Bennett, PhD

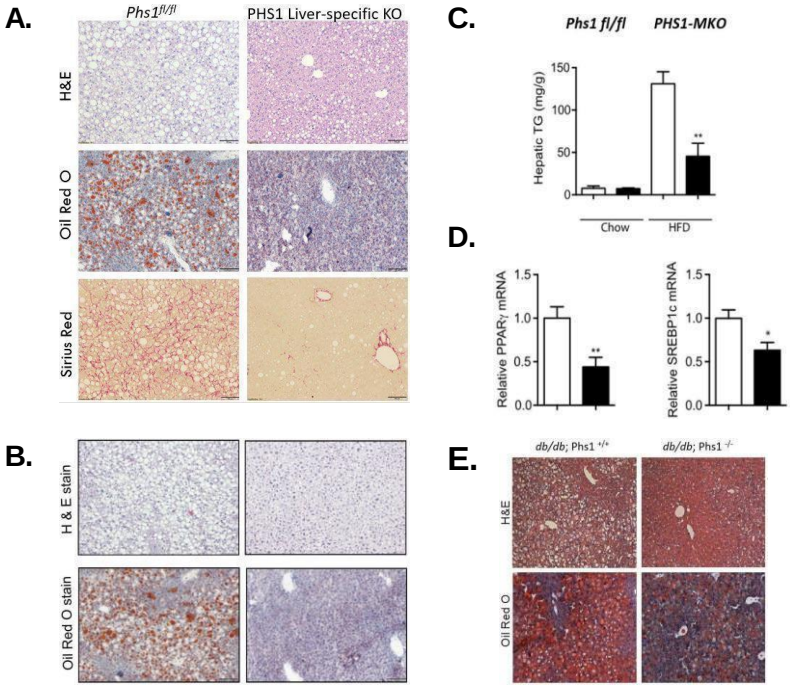
Background:

- Non-Alcoholic Steatohepatitis (NASH) is a serious liver condition induced by a high-fat diet (HFD), leading to elevated liver triglycerides and liver damage.
- Current treatments for NASH are limited and lack efficacy in significantly preventing disease progression.
- New research demonstrates that tissue-specific knockout (KO) of the "Phs1" phosphatase prevents HFD-induced NASH, providing a novel therapeutic target.

Indications: Non-Alcoholic Steatohepatitis (NASH), liver diseases, fibrosis

Innovation & Asset:

- **Effective KO Protection:** Prevents HFD-induced NASH in global and liver-specific KO mouse models.
- **Reduces Liver Triglycerides:** Decreases liver triglyceride levels and related mRNA expressions (PPARγ, SERP1c).
- **Broad Validity:** Demonstrated efficacy in genetically obese mice.
- **Target Drugability:** Identified and successfully targeted allosteric site for Phs1 phosphatase.
- **IP:** US Patent 11,504,373 and multiple national patents issued



Phs1 is required for the development of NASH across multiple mouse models.

(a) Liver-specific Phs1 knockout (KO) mice on a choline-deficient, amino acid-defined (CDAA) diet fail to develop NASH.

(b) Liver-specific Phs1 KO mice are protected against high-fat diet (HFD)-induced NASH.

(c) Phs1 KO reduces hepatic triglyceride accumulation.

(d) Hepatic mRNA levels of PPARγ and SERP1c are decreased in Phs1 KO mice.

(e) Genetically obese (ob/ob) Phs1 KO mice are protected from NASH development.

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YALE VENTURES

YV6925:Molecular Therapies of Atherosclerosis

PARTNERED

Principal Investigator: Michael Simons, M.D.

Background:

- Atherosclerosis causes the majority of cardiovascular diseases, current therapies (statins) only slow the disease.
- Targeting TGF, FGF, and let-7 miRNA signaling in the endothelium can reduce atherosclerotic plaques.
- Genetic proof of concept demonstrated in mice with endothelial-specific TGFR1/R2 knockout.

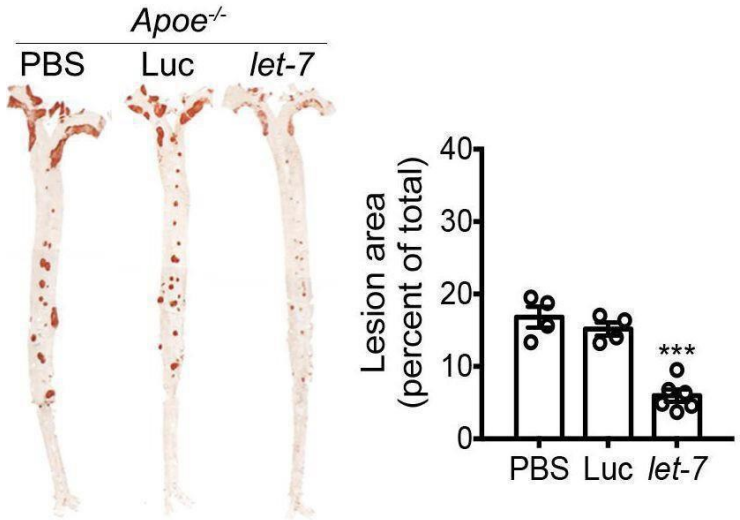
Indications: Atherosclerosis, CAD/MI/Angina, Stroke, Peripheral vascular disease

Innovation & Asset:

- **miRNA Therapy:** Endothelium-specific let-7 miR delivery.
- **Plaque Reduction:** Effectively reduces the size of atherosclerotic plaques.
- **Burden Decrease:** Decreases overall atherosclerosis burden.
- **Validated in Mice:** Genetic proof of concept in endothelial-specific TGFR1/R2 knockout mice.
- **Supporting Data:** Additional validation from human samples.

References: Nat Metab 2019 Sep;1(9):912-926

IP : US patent: 11,326,167



Endothelium-specific delivery of let-7 miR reduces atherosclerosis: ~ 60% reduction in total plaque burden in Apoe-/-

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YALE VENTURES

YV6785: Orally-delivered nanoparticles

PARTNERED

Principal Investigator: Tarek Fahmy, Ph.D.

Polymeric Bile Acid Formulations for Targeted Delivery

- A new class of polymer biomaterials (PUDCA) that are selectively taken up and retained in the pancreatic, hepatic and colon microenvironment.
- Formulated as orally administered, safe and biodegradable nanoparticles.
- Unique properties: encapsulates drugs and/or agents, pH-responsive, enables sustained release.
- **Indications:** targeted delivery of drugs and tracking/imaging agents to sites of pancreatic, hepatic and colonic inflammation. For therapy and diagnostic uses
- **IP status:** WO2017041053A1, and related Nat'l phase in US, EP, CA, CN, AU
- **Publications:** Unpublished work

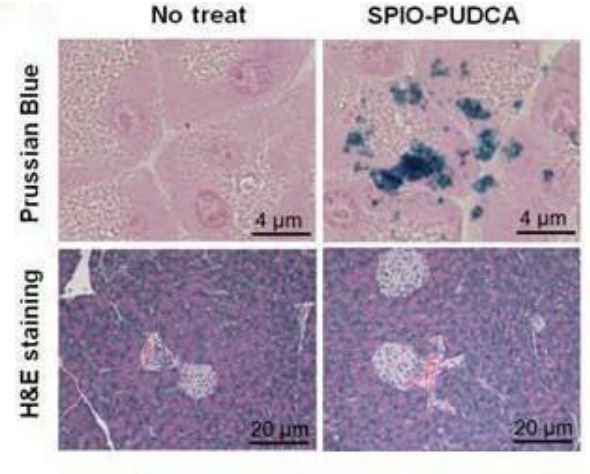

FIG. Histology images of pancreatic sections from mice that were orally treated with PBS or PUDCA nanoparticles containing iron oxide (SPIO-PUDCA). Iron Oxide is assayed using the Prussian Blue stain which appears distinct in the pancreas.

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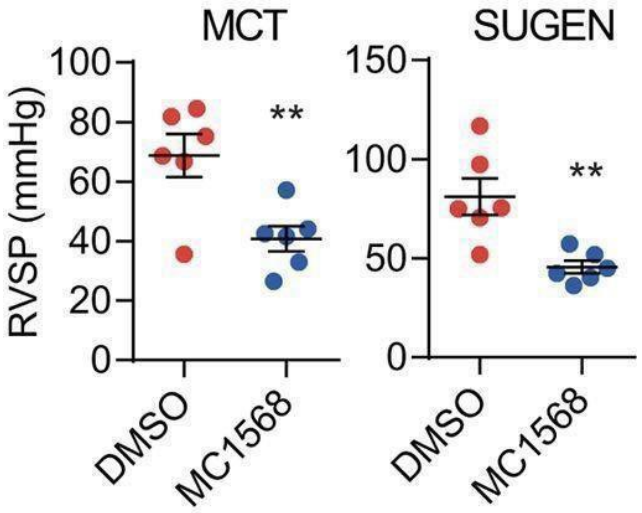
YV6370: Therapeutic for Pulmonary Arterial Hypertension

Principal Investigator: Hyung Chun, M.D.

HDAC Inhibitors for Treatment of PAH

- Pulmonary arterial hypertension (PAH) has limited treatment options with 40-50% mortality within 3 years of diagnosis.
- It remains a critical unmet medical need. The global market for PAH is expected to grow to over $3.5 billion by 2016.
- Augmentation of MEF2 activity holds a potential therapeutic value in PAH.
- HDAC IIa inhibition enhances MEF2 activity, shows efficacy in rodent models of PAH.
- Selective HDAC inhibition should avoid the potential adverse effects of broad spectrum HDAC inhibition in PAH.
- **Reference:** Kim et al. (2015) Circulation.
- **Issued Patents:** 10,213,422



Right ventricular systolic pressure (RVSP) measurement in rats received either vehicle (DMSO) or MC1568, an HDAC class IIa specific inhibitor. MC16568 rescues experimental mouse models of pulmonary hypertension (MCT, SUGEN).

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YV6368: Thyroid hormone for Fibrotic Lung Diseases

PARTNERED

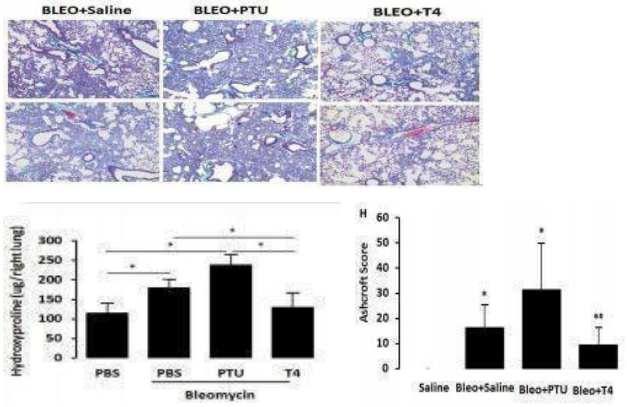
Principal Investigator: Naftali Kaminski, M.D.

Thyroid hormone as a novel therapeutic agent in fibrotic lung diseases

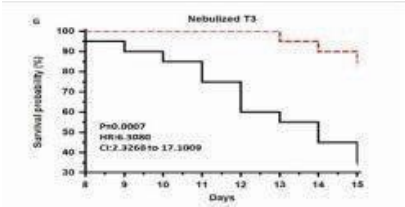
- Idiopathic pulmonary fibrosis (IPF) is a lethal fibrotic lung disorder. The median survival of patients with IPF is 3.5-4

  years from initial diagnosis, irrespective of treatment.
- **Innovation:**
  - Inhaled or aerosolized delivery of thyroid hormone to the lung – preliminary results demonstrate thyroid hormone resolves pulmonary fibrosis in animal models and increases survival.
- **IP Status:** PCT/US 15/317,276

Resolving Fibrosis



Increasing Survival



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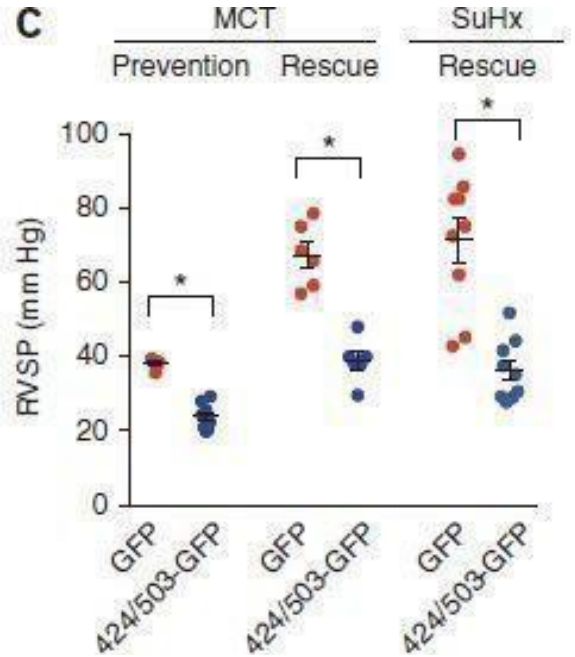
YALE VENTURES

YV5799: Novel Therapeutic for Pulmonary Arterial Hypertension

Principal Investigator: Hyung Chun, MD, FAHA

- Pulmonary arterial hypertension (PAH) has limited treatment options with 40-50% mortality within 3 years of diagnosis.
- Identification of novel therapeutic targets remains a critical unmet medical need for this disease.
- The global market for PAH is expected to grow to over $3.5 billion by 2016[1].
- MicroRNAs (miRs) 424 and 503 are effective in human and animal models of PAH (see figure).
- miRs 424 and 503 may be the basis for effective therapeutics for PAH.
- **Reference:** Kim et al., 2013 Nature Medicine
- **Patent:** US20140155459A1



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Therapeutics:

Inflammatory and
Autoimmune disorders,
Immunomodulation

YV8972: Novel Small-Molecule Protein Degraders Targeting GSK-3 and β-catenin

Principal Investigator: Ya Ha, PhD

Background:

- Protein kinase GSK-3 is implicated in multiple diseases, including COVID-19, cancer, bipolar disorder, Alzheimer's disease, diabetes, chronic inflammatory diseases, and myotonic dystrophy. Most GSK-3 inhibitors target the kinase's binding sites for ATP or protein substrates, which have various limitations.
- **β-catenin is an important oncogene aberrantly activated in many human cancers.**
- A novel pharmacological tool combining **two FDA-approved oral drugs elicits autophagy to selectively degrade** GSK-3 **and β-catenin,** providing a unique approach for disease treatment.

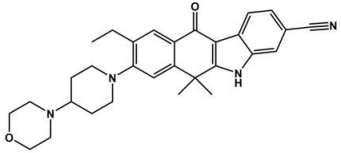
Indications: COVID-19, cancer, bipolar disorder, Alzheimer's disease, diabetes, chronic inflammatory diseases, myotonic dystrophy

Innovation & Asset:

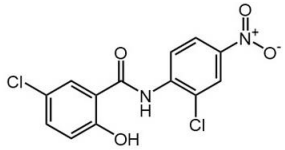
- **Novel Approach**: Combining FDA-approved drugs niclosamide and alectinib (or gilteritinib)
- **Effective Downregulation**: Synergistically induces degradation of GSK-3 and β-catenin in live cells through autophagy
- **Broad Application**: Potentially effective across multiple disease areas including COVID-19 and cancer
- **Improved Efficacy**: Directly reduces biological activity by suppressing target protein levels

IP: U.S. Provisional Patent filed May 23, 2024

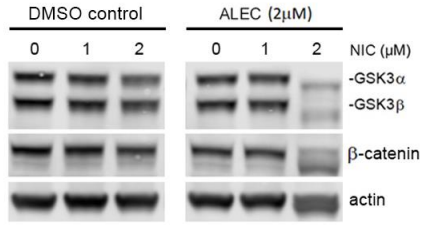
[Pre-print publication]

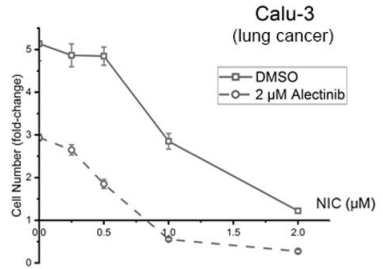


Alectinib



Niclosamide





In the presence of 2μM alectinib (ALEC), niclosamide (NIC) suppresses GSK-3 and β-catenin protein levels and inhibits Calu-3 (lung cancer cell) growth in a dose-dependent manner.

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YALE VENTURES

YV8731: HIF Inhibition for the Treatment of Cutaneous Lupus

Principal Investigator: Alicia Little, MD, PhD

Background:

- Hypoxia-inducible factor-1 (HIF-1) upregulation is responsible for the inflammatory T-cell phenotype in lupus nephritis (Chen et al., Sci Trans Med, 2020), but its role in cutaneous disease was previously undefined.
- Current treatments for lupus nephritis focus on suppressing the immune system, with significant limitations including non-specificity and side effects.
- This new technology identifies a novel, druggable pathway (HIF-1) implicated in cutaneous lupus erythematosus, targeting the specific upregulation responsible for inflammation.

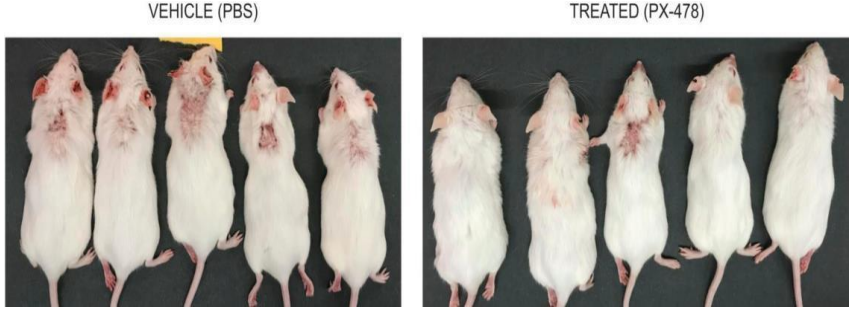
Indications: Cutaneous lupus erythematosus (CLE)

Innovation & Asset:

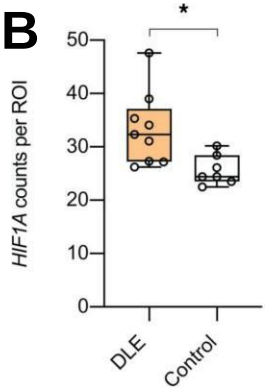
- **Novelfocus**: Druggable pathway implicated in cutaneous lupus erythematosus.
- **Efficacy**: Murine models show reduced skin disease with HIF-1a inhibition (A).
- **Human relevance**: Similar molecular profile in human discoid lupus erythematosus.
- **Targeted approach**: Potential for specific HIF-1a targeting (B).
- **Clinical potential**: New therapeutic approach for skin disease in lupus.

IP: US patent filed: 18/785,392

A



B



A. Representative images of clinical disease in 20-week-old MRL/lpr mice after 4 weeks of treatment with either PX-478 (small molecule HIF-1a inhibitor) or vehicle control (PBS).

B. Normalized HIF-1a expression per region of interest (ROI) in discoid lupus erythematosus (DLE) or healthy control skin (n = 3 patients; n = 3 ROIs per patient), as characterized by NanoString GeoMx Digital Spatial Profiling.

Little et al, *JCI Insight*, 2023

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YALE VENTURES

YV8680: CAR-mast cell therapy for solid tumor

Principal Investigator: Xiaolei Su, PhD

Background:

- CAR-T cell therapy shows limited efficacy on solid tumors due to poor infiltration, exhaustion, and low persistence in an immune-suppressive tumor microenvironment (TME).
  Indications: Seeking alternative cell carriers for CAR

Rationales: Mast cells are ideal candidates because 1) they release cytotoxic factors that induce target cell death, (2) they release chemokines and cytokines that recruit T & NK cells into the tumor and remodel TME, (3) they are long-lived (up to years) in tissues and could confer a sustainable anti-tumor effect.

Innovation & Asset:

- **CAR-Mast Cells:** Developed for solid tumors.
- **Antigen Activation:** Specifically activated by tumor antigens.
- **Chemokine Release:** Attract T and NK cells to the tumor.
- **Direct Cytotoxicity:** Direct killing of cancer cells by CAR-mast cells (B)
- **In Vivo Efficacy:** Anti-tumor effects by CAR-mast cells in mouse xenograft models (C-D)
- **Safety Profile:** No tissue toxicity or anaphylaxis observed in mouse models.

IP: PCT/US2024/029466

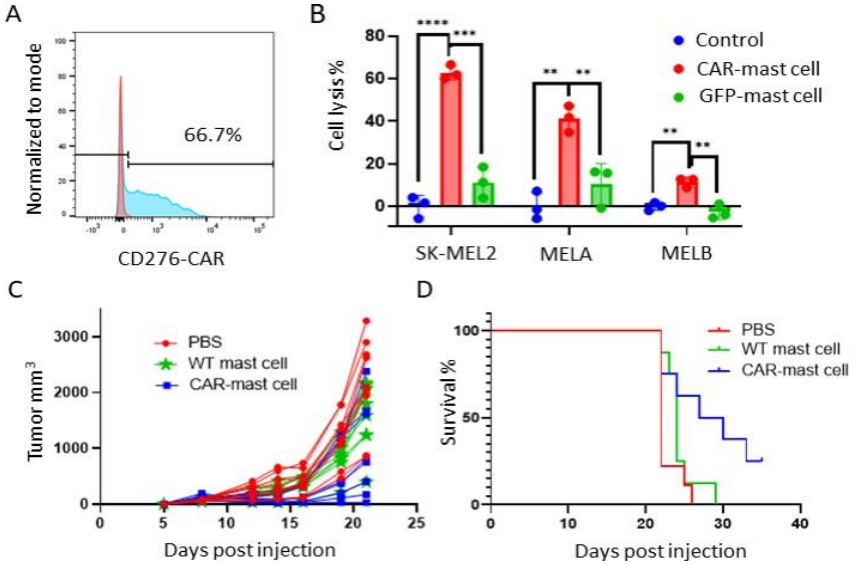

Fig.1 Cytotoxicity of anti-CD276 (B7H3) CAR-mast cells. A) Expression of CD276 CARin mast cells. **B)** CAR-mast cells were incubated with CD276+ human melanoma cells at an E:T= 5:1. **C)** Monitoring tumor growth in C57BL/6 mice xenografted with MC38-CD276+ cells. Each mouse received 5x10^6 MC38 cells at Day0, and 2.5 x10^6 mast cells at Day8 and Day14. **D)** Mice survival following CAR- mast cell treatment.

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YV8639 : Best in Class Lipid Radical Trapping Antioxidant Small Molecule Ferroptosis Inhibitors

Principal Investigator: Dianqing (Dan) Wu, PhD

Background:

- Ferroptosis is the leading type of cell death in pathological conditions.
- Ferroptosis is characterized by iron accumulation and lipid peroxidation.
- This new technology utilizes lipid radical trapping antioxidants to inhibit ferroptosis, protecting of organs and tissues from cell death damage from lipid peroxidation.

Indications: Acute lung injury, Acute kidney injury, Inflammatory bowel disease

Innovation & Asset:

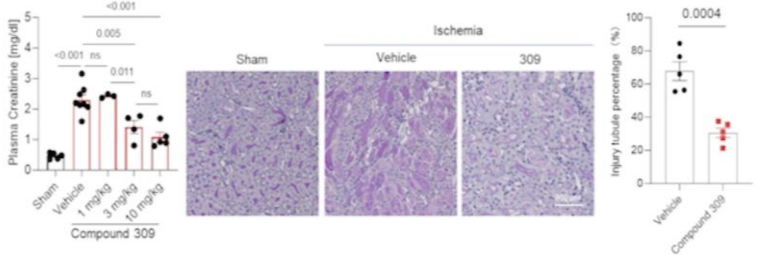
- **High Potency:** Exhibits nanomolar IC50 values for ferroptosis inhibition.
- **Stability:** Improved pharmacokinetics and stability over current alternatives.
- **Oral & IV Formulations:** Available in both oral and intravenous forms.
- **Broad Applicability:** Effective for multiple diseases involving ferroptosis.
- **Clinical Potential:** Demonstrated efficacy and safety in preclinical models.

IP: Patent application filed.

Learn More: Yale Life Sciences PitchFest

Pharmacokinetic Parameters Following IV and PO Administration

PK parameter	Compound code	LFPI-309	LFPI-336	LFPI-338
IV (3 mg/kg)	AUC_{last} (hr*ng/mL)	5633	4426	925
	$t_{1/2}$ (hr)	5.05	5.91	0.456
	C0 (ng/mL)	17782	8798	2226
PO (10 mg/kg)	AUC_{last} (hr*ng/mL)	3165	5460	404
	$t_{1/2}$ (hr)	4.49	3.58	1.85
	C_{max} (ng/mL)	709	1584	405
	F (%)	16.9	36.6	13.4



Compound 309 Mitigates Renal Injury in Ischemia-Reperfusion AKI. This figure demonstrates the protective effects of Compound 309 in a murine acute kidney injury (AKI) model induced by bilateral ischemia-reperfusion. **(Left)** Plasma creatinine levels significantly increase in vehicle-treated ischemic mice, while Compound 309 (10 mg/kg) reduces levels by >50%, indicating improved renal function. **(Middle)** H&E-stained kidney sections show extensive tubular damage in vehicle-treated mice, whereas Compound 309 preserves renal architecture (scale bar = 100 µm). **(Right)** Quantification of tubular injury confirms a significant reduction in kidney damage with Compound 309 (p = 0.0004), supporting its potential nephroprotective effects.

YV8450: Novel Food Allergy Treatment Adjunct

Principal Investigator: Ruslan Medzhitov, PhD

Background:

- Food allergies affect 10% of US population
- No approved treatment options exist. Experimental oral immunotherapy has low efficacy and high risk of adverse effects.

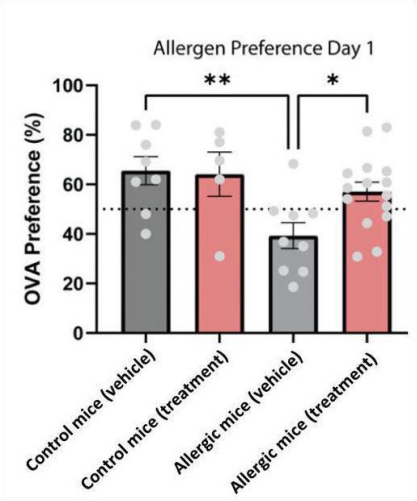
Indications: Suppression of food allergic reactions

Innovation & Asset:

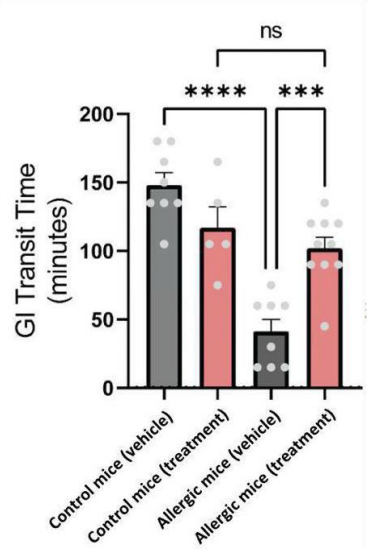
- **Novel Method:** Uses a known, orally-active small molecule inhibitor of a key inflammatory enzyme.
- **Efficacy in Mice:** Reduces avoidance of allergen (**A**) and ameliorates allergen-induced diarrhea (**B**)
- **Comprehensive Benefits:** Normalizes temperature drop, mast cell hyperplasia, and intestinal pathology (dns).
- **Safety Advantage:** No risk of serum sickness, no injections needed, and cost-effective compared to antibody pre-treatments.

IP: PCT/US23/84085

A Mice sensitized to ovalbumin (allergic mice) show decreased consumption of ovalbumin compared to controls. Treatment with the drug reverses the ovalbumin avoidance in allergic mice.



B Mice sensitized to ovalbumin (allergic mice) show decreased gastrointestinal transit time when given ovalbumin. Treatment with the drug slows the transit time to control levels.



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YV8415: Novel peptide to promote neovascularization in critical limb ischemia

Principal Investigator: Mehran M. Sadeghi, MD

Background:

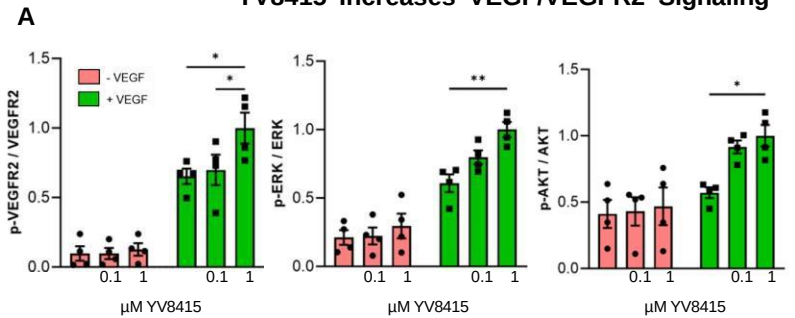
- 2.5M people in the U.S. have CLI, the end stage of peripheral artery disease
- CLI has a 50-60% 5-year mortality and is estimated to contribute ~$4B in annual U.S. health care costs

Indications: Critical limb ischemia, peripheral arterial disease, wound healing

Innovation & Asset: Novel Humanized Peptide

- YV8415 significantly enhances VEGF signaling, resulting in increased angiogenesis
- YV8415 has the potential to improve outcomes for patients with CLI through revascularization

IP: PCT/US2024/56265



(A) Western blot quantification of the effect of concentration of YV8415 on VEGF/ VEGFR2 signaling. *p < 0.1, **p < 0.01.

(B) Examples and quantification of CD31 whole mount immunostaining (in red) of mouse cornea tissue. The white dashed circles represent the location where the sustained-release pellets were implanted. Scale bar: 500 µm. ****p < 0.0001.

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YV8210: Treating Inflammatory Diseases through a Novel Pathwaywith L-Ornithine

Principal Investigator: Jason Crawford, PhD & Richard Flavell, PhD

Background: Laccase domain-containing 1 protein (LACC1)

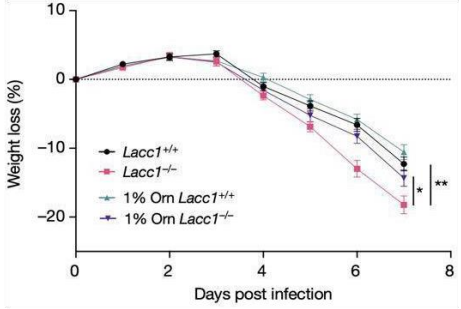
- **Regulates immunometabolism in myeloid cells**
- **Mutations associated with Crohn's disease, systemic juvenile idiopathic arthritis, ankylosing spondylitis, leprosy risk**

Indications: Bacterial infections, Inflammatory conditions

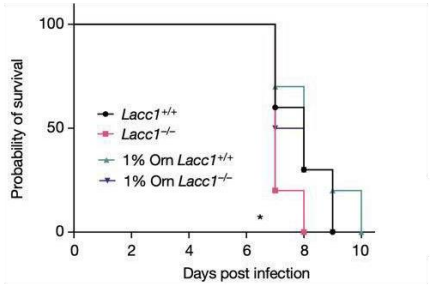
Innovation & Asset: Rescuing LACC1 deficiency with L-Ornithine

- **Decreases pro-inflammatory cytokine release from macrophages (in vitro, dns)**
- **Mitigates weightloss (A), improvessurvival (B), and decreases bacterial burden (C) in LACC1-KO mice**
- **Simple and economical production**

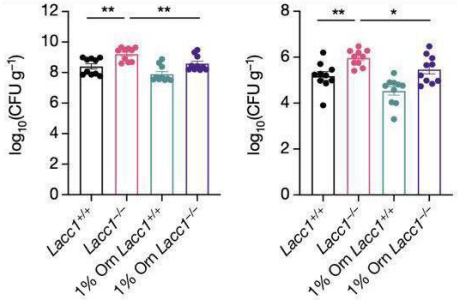
A L-Ornithine supplementation rescues weight in LACC1-KO mice after S. Typhimurium infection.



B L-Ornithine supplementation rescues survival in LACC1-KO mice after S. Typhimurium infection.



C In LACC1-KO mice, L-Ornithine supplementation decreases bacterial burden in caecum (left) & spleen (right) tissue at 6 days after infection with S. Typhimurium.



IP: PCT/US2023/067995

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YALE VENTURES

YV7690: Lovastatin Ointment Monotherapy as a Treatment for Porokeratosis

PARTNERED

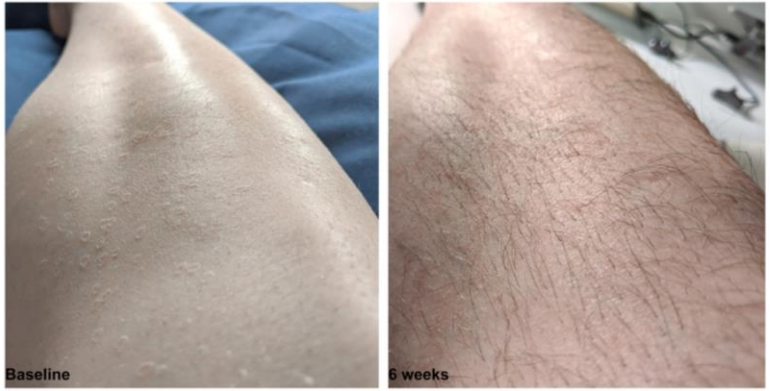
Principal Investigator: Keith Choate, MD

Background:

- Porokeratosis affects approximately 7-10% of people with disseminated superficial actinic porokeratosis (DSAP), a premalignant skin condition characterized by abnormal keratinization.
- Traditional treatments include lesion destruction techniques like cryotherapy and topical therapies (e.g., steroids, vitamin D analogs), which are often ineffective and costly.
- A topical formulation of 2% lovastatin has shown promising results in reducing the scaling and inflammation associated with porokeratosis by targeting the mevalonate pathwa thus offering an efficient and cost-effective alternative.
- **Indications:** Porokeratosis including DSAP, PPPD, LP, actinic keratosis, superficial non-melanoma skin cancer

Innovation & Asset:

- **Targeted Therapy**: Specific action on the mevalonate pathway upstream of MVD enzyme
- **High Efficacy**: Significant reduction in scaling and erythema.
- **Good Safety Profile**: Demonstrated safety profile of lovastatin and cholesterol.
- **Versatile Application**: Applicable to various porokeratosis subtypes.



Six weeks of therapy with lovastatin 2% ointment twice daily resulted in the complete reduction in scaling in a patient with disseminated superficial actinic porokeratosis (DSAP) with heterozygous *MVD* c.70+5G>A mutation

IP: US-2022-0168270-A1 filed 12/10/21

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YALE VENTURES

YV7611/7612: Treatment of Diseases Associated with Increased Levels of TET and TGF

Principal Investigator: Yingqun Huang, MD, PhD

Background:

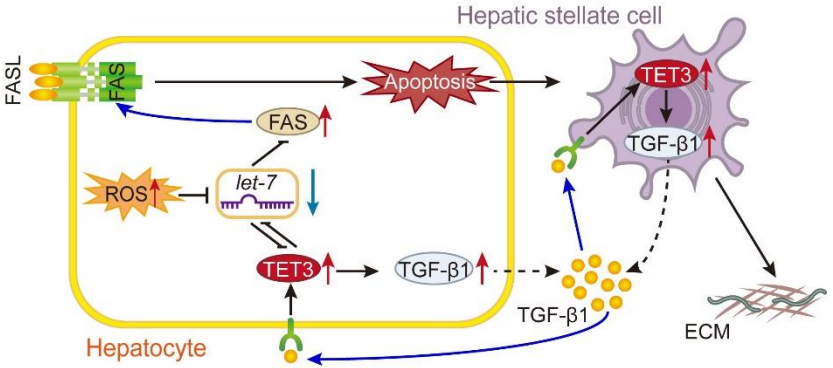
- Chronic inflammation and fibrosis are a major cause of morbidity and mortality, affecting millions worldwide, particularly in chronic liver diseases such as metabolic dysfunction-associated steatohepatitis (MASH).
- Current treatments for chronic inflammation and fibrosis are limited, as they do not halt or reverse disease progression.
- This technology targets novel proteins (TET3 and TGF), reducing their levels or activity to treat fibrosis.

Indications: endometriosis and MASH

Innovation & Asset:

- **Multi-pathway inhibition:** Targets TET3 and TGF pathways, key drivers of inflammation and fibrosis.
- **Biomarker-driven:** Uses novel biomarkers for treating inflammation-related diseases.
- **Broad application:** Effective against multiple inflammatory diseases.
- **Reversible fibrosis:** Potential to halt and reverse fibrotic progression, addressing unmet medical needs

IP: PCT/US2020/26290



Liver fibrosis is driven by a deleterious cycle involving TET3, TGF-β, and *let-7*. Reduction of *let-7* levels due to stress causes TET3 and FAS to increase, leading to liver cell death. This activates hepatic stellate cells (HSCs), which produce more TGF-β1 and scar tissue. The rise in TGF-β1 boosts TET3 further, creating a feedback loop. This cycle worsens over time, causing more cell death, HSC activation, and fibrosis.

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YV7602: New target for the treatment of Autosomal Dominant Polycystic Kidney Disease

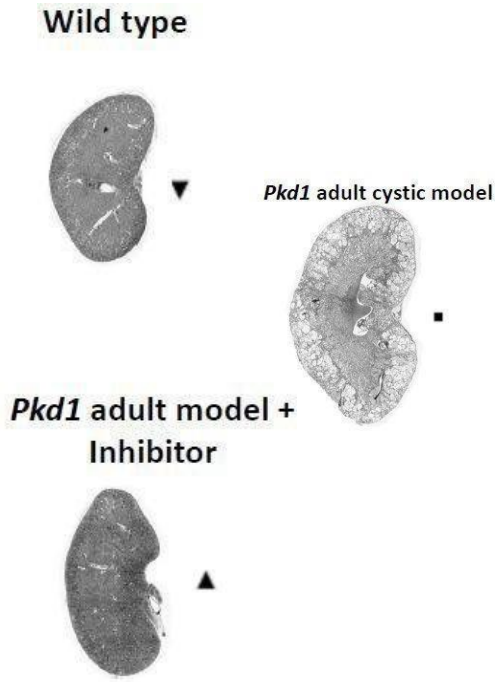
Principal Investigators: Stefan Somlo, MD, Sorin Fedeles, PhD, MBA

Background

- Autosomal Dominant Polycystic Kidney Disease (ADPKD) affects >600,000 in US population; 12.5 M worldwide
- ~4% of prevalent End-Stage Renal Disease (ESRD)
- ADPKD has **orphan condition designation** (2012) with estimated prevalence in US 1:2000
- One **approved therapy:** Tolvaptan (Jinarc) – approved April, 2018
- Targets low level proliferation and secretion in cysts originating from collecting duct; unknown long term efficacy and significant side effects including liver toxicity (Hy's law)

Innovation

- Identified the Ireα-Xbp1 pathway as a modulator of cyst growth
- Inhibition of this pathway at the genetic level slows down disease progression in orthologous animal models through specific apoptosis of mutant cells
- Generated a pre-clinical efficacy package around a novel use for an Ireα inhibitor previously tested in human trials
- Starting a high-throughput screen for novel compounds targeting Ireα-Xbp1 pathway



IPstatus: PCT/US22/72926

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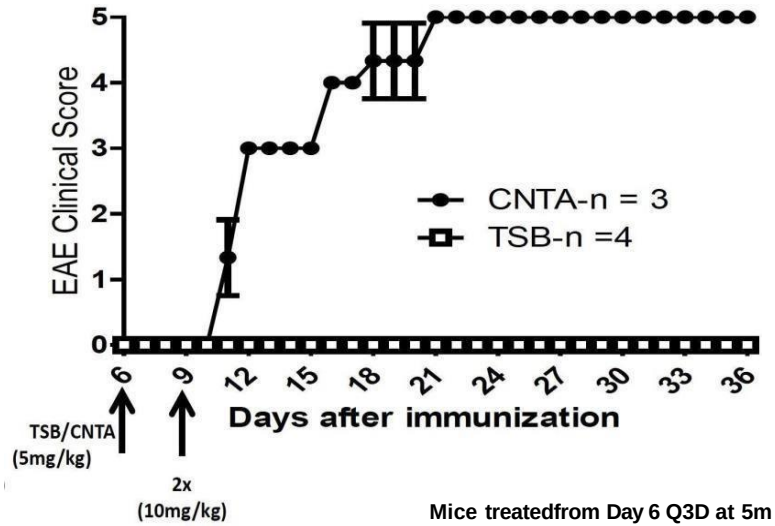
YALE VENTURES

YV7398: Reduction of IL-17A with an Inhibitor of miR466l-3p Binding to IL-17A mRNA

Principal Investigator: Jeffrey Bender

- The microRNA miR466l-3p stabilizes IL-17A mRNA thereby increasing IL-17A levels.
- IL-17A plays a pathogenic role in multiple inflammatory diseases (e.g., MS, IBD, Psoriasis).
- A nucleotide has been developed that selectively blocks this miR466l-3P site on the IL-17A mRNA, and reduces IL-17A levels.
- In vivo proof of concept of this therapeutic approach has been demonstrated in two mouse models of MS.
- A provisional patent application has been filed.

miR466l-3p/IL-17A Target-Site Blocker (TSB) in a progressive EAE mouse model of MS. (2D2 Transgenic)



Mice treatedfrom Day 6 Q3D at 5m g/kg i.p. except for a 10mg/kg dose on Day 9.

YV6474: Treatment of Type II Inflammatory Disorders by Inhibiting Dkk-1 Activity

- Dr. Bothwell and his colleagues at Yale have discovered a novel role of Dkk-1 in type 2 immune responses.
- Upon environmental challenges, Dkk-1 is secreted from and circulated by platelets to facilitate leukocyte migration and polarize immune responses by inducing Th2 cell polarization.
- Functional inhibition of Dkk-1 protects mice from chronic type 2 inflammation in house dust mite (HDM)-induced asthma and Leishmania major cutaneous infection.
- Dkk-1 is an attractive target for controlling type 2 immune responses.
- **Intellectual property**: A patent application has been filed
- **Reference:** Chae, Wook-Jin et al. (2016) Immunity. The Wnt antagonist Dickkopf-1 promotes pathological type 2 inflammation.

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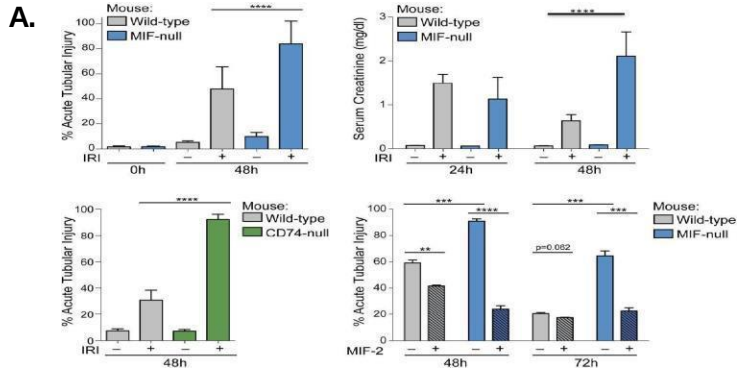
YV5557: MIF-2 for Acute Kidney Injury (AKI)

Principal Investigator: Bucala, Young, Moeckel

Recombinant Biologic to Prevent & Treat AKI

- **MIF-2** (aka D-DT) has utility for the prevention and repair of ischemia/reperfusion AKI.
- **Validity of Human Clinical Hypothesis:** Geneticallycharacterized subset of cardiac surgery patients suffer AKI.
- **Efficacy/Safety**
  - **Mouse:** MIF-2 treatment results in AKI repair (**A/B**).
  - **Mouse:** MIF-2 stimulates multiple cell repair mechanisms. (**C**).
- **Pre-clinical studies**
  - **Mouse:** High therapeutic dose without toxic side effects.
  - **Pig:** Initial PK/PD studies completed.
- **Manufacturing** This 37.5 kD MIF-2 protein homotrimer (**D**) has been scaled up for porcine studies (CRO; E. coli).
- **IP:** Multiple national patents issued; issued US patent: 9,308,255



Immunohistochemistry staining for Cyclin D1 (cell proliferation & regeneration) 48 h after I/R injury.

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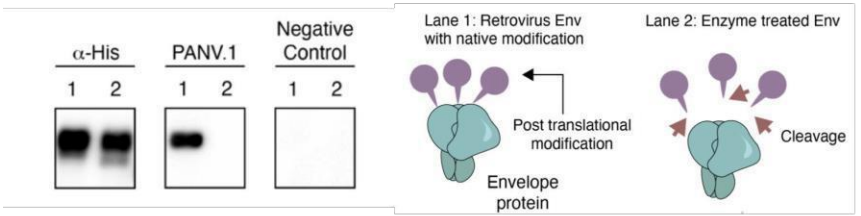
Vaccines & Infectious Disease

YV8246: PANV.1: A Monoclonal Antibody Targeting Epitopes in Multiple Viruses

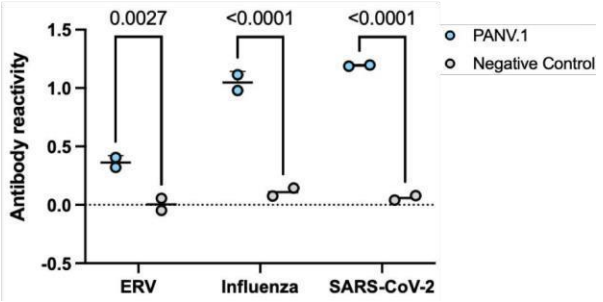
Principal Investigator: Akiko Iwasaki, PhD

- **Background:** Viral outbreakspresent a significantglobal healthchallenge
  - Virus-specific treatments are slow to develop and often not available in early outbreaks
- **Innovation & Asset:** Pan-viral monoclonal antibody against a novel target
  - Specific for post-translational glycan modification on viral envelope proteins(**A**)
  - Reactive against multiplevirus types (**B**)

A PANV.1 recognizes a post-translational modification on viral envelope proteins.



B PANV.1 demonstrates pan-viral potential. PANV.1 reacts with endogenous retroviruses, influenza virus, and SARS-CoV-2



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YALE VENTURES

YV8038: 20 nM SARS-CoV-2 Protease Inhibitors

Principal Investigator: William Jorgensen

Structure-based design of M_{pro} Antagonist

- non-peptidic, non-covalent, inhibitors of the SARS CoV-2 main protease (Mpro) (Table 1).
- YV8038 inhibitors have 0.2 μM activity in infected cells, while remdesivir is 1.0 μM
- Weak binding non-antiviral approved drug (Table 1/Cmpd 1) optimized for Mpro inhibition (Table 1/Cmpds 18 - 25).
- High-resolution co-crystal structures of complexes (Figure 1).
- Demonstrated anti-viral properties in vitro (Table 2). Synergy with remdesivir (Figure2)
- Drug-like properties & commercially viable synthetic routes

Figure 1

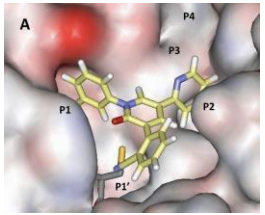


Figure 2

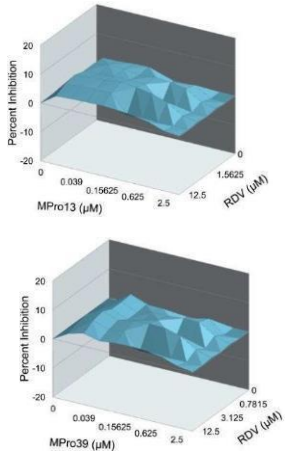


Table 1

Table 1. Measured activities for inhibition of SARS-CoV-2 M^{pro}.

Cmpd	IC_{50} (μM)	Cmpd	IC_{50} (μM)	Cmpd	IC_{50} (μM)
1	100-250[a]	11	0.120 ± 0.016	21	0.018 ± 0.002
2	9.99 ± 2.50	12	0.25 ± 0.09	22	0.036 ± 0.004
3	6.38 ± 1.21	13	0.19 ± 0.03	23	0.020 ± 0.005
4	4.02 ± 1.36	14	0.128 ± 0.015	24	0.037 ± 0.004
5	0.14 ± 0.02	15	0.110 ± 0.013	25	0.025 ± 0.003
6	0.47 ± 0.02	16	0.100 ± 0.007	26	0.170 ± 0.022
7	0.28 ± 0.05	17	0.110 ± 0.035	27	0.120 ± 0.006
8	0.51 ± 0.02	18	0.024 ± 0.007		
9	1-10[a]	19	0.037 ± 0.007		
10	1.20 ± 0.03	20	0.036 ± 0.003		

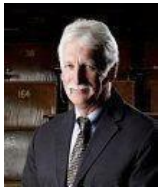
[a] Fluorescence of compound interfered with assay.

Table 2

Enzyme Inhib. (IC_{50}), Anti-SARS-CoV-2 Activity (EC_{50}), and Cell Toxicity (μM).

Compound	IC_{50}	EC_{50} Replicon	EC_{50} Plaque	CC_{50} Vero E6	CC_{50} NHBE
remdesivir	-	1.0	0.77[a]	72 ± 28	41 ± 2
5 Mpro13	0.140	1.5	1.5	22 ± 7.2	20 ± 2
26 Mpro39	0.170	1.8	0.98	>100	>100
27 Mpro48	0.072	1.2	ND[b]	22± 8	25± 5
Mpro57	0.077	0.3	ND[b]	82	>100
Mpro60	0.075	0.8	ND[b]	>100	ca. 95
Mpro61	0.053	0.2	ND[b]	ca. 100	ca. 100

[a] Ref. 24. [b] ND = not determined



Lead Innovator
William L. Jorgensen
Sterling Professor
Of Chemistry
Homepage

YV7981: Compounds and Compositions for Disrupting Programmed Ribosomal Frameshifting

Principal Investigator: Junjie Guo, PhD

Background:

- Programmed ribosomal frameshifting is a prevalent and critical feature among RNA viruses.
- Dr. Junjie Guo's lab developed a platform to rapidly identify chemical modifiers of ribosomal frameshifting.
- Identified compounds can enhance or suppress ribosomal frameshifting in SARS-CoV-2 and other beta coronaviruses.

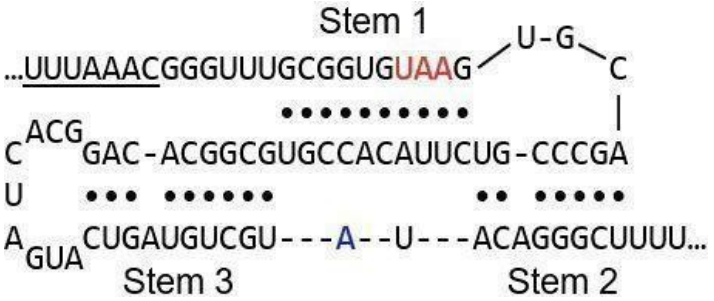
Indications: SARS-CoV-2, other beta coronaviruses

Innovation & Asset:

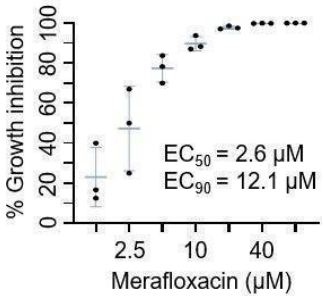
- **Ribosomal Frameshifting:** Technology targets a critical viral replication mechanism.
- **Platform Capability:** Rapid identification of chemical modifiers.
- **Inhibition Efficacy:** Frameshift inhibition significantly reduced SARS-CoV-2 replication in Vero E6 cells.
- **Versatility:** Potential application across multiple beta coronaviruses.
- **Therapeutic Potential:** High impact on public health with antiviral capabilities.

Reference: Sun et al., bioRxiv (2020) https://doi.org/10.1101/2020.10.21.349225

IP: PCT/US21/047163



Figures showing the proposed secondary structure of SARS-CoV-2 frameshift-stimulating element (top) and the antiviral activity of merafloxacin, our newly discovered frameshift inhibitor, against SARS-CoV-2 in Vero E6 cells (bottom).



Yale

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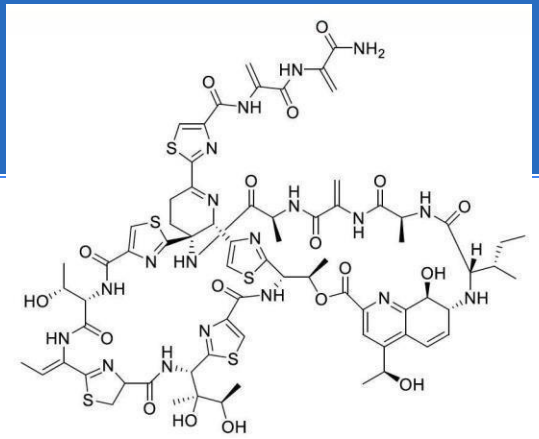
YALE VENTURES

YV7705: Novel Thiostrepton analogs with Improved solubility



Principal Investigator: Jon Ellman, PhD

Background:

- Thiostrepton (shown to the right) is a natural product with potent activityagainst Gram positive bacteria, including MRSA.
- Clinical use of Thiostrepton in humans however is precluded by the compound's poor aqueous solubility.
- Semi-synthetic analogs have been developed to enhance solubility while retaining antibacterial activity.

Indications: MRSA, Gram-positive bacterial infections

Innovation & Asset:

- **Thiostrepton Analogs:** Semi-synthetic versions with improved solubility.
- **Antibacterial Efficacy:** Retains potent activity against Gram-positive bacteria.
- **Optimization Ongoing:** Additional analogs being evaluated for clinical utility.
- **Solubility & Potency:** Focus on optimizing both characteristics.

Reference: Cobalt (III)-Catalyzed C-H Amidation of Dehydroalanine for the Site-Selective Structural Diversification of Thiostrepton. R.J. Scamp, E. de Ramon, E.K. Paulson, S.J. Miller & J.A. Ellman. Angew. Chem. Int. Ed. 59: 890 (2020) https://onlinelibrary.wiley.com/doi/10.1002/anie.201911886

IP: PCT/US2020/032565

COMPOUND	MIC (ug/ml)		SOLUBILITY (ug/ml)
	Staph. Aureus MSSA	Staph. Aureus MRSA	
Thiostrepton	0.06	0.12	3.0
Analogs			
RJS-01	2	4	83
RJS-04	0.5	0.5	16.2
RJS-06	0.5	1	28
RJS-10	1	1	19
RJS-12	1	1	20
RJS-15	0.5	1	4.3
RJS-16	16	16	11

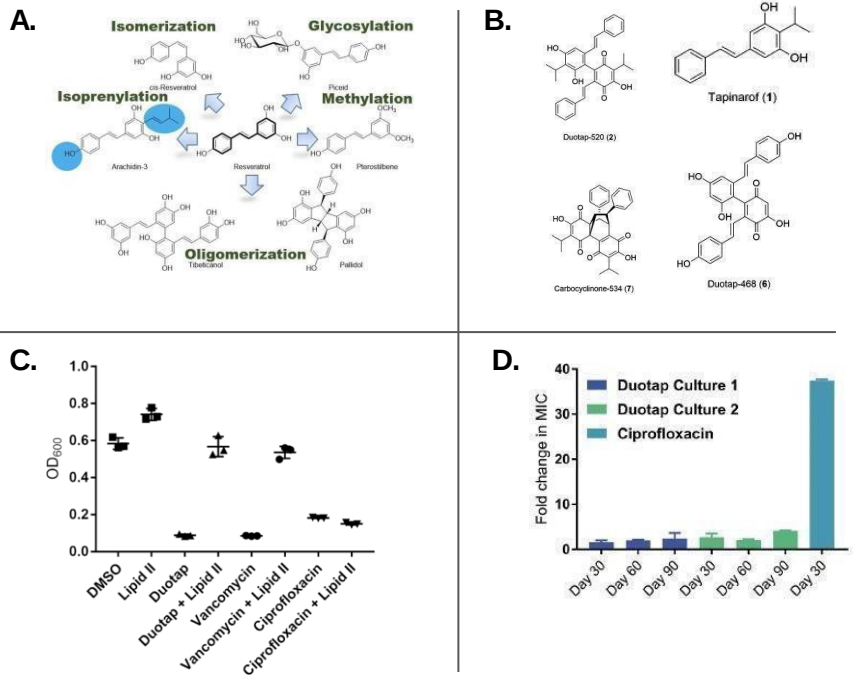
YV7643: Novel Stilbenes for immuno-dermatology and antibiotics (MRSA/VRE)

Principal Investigator: Jason Crawford

Duotap is a novel active derivative of tapinarof

- **Stilbenes are readily derivatized for optimization to purpose (A)**
  - Duotap is a tractable scaffold for further derivatization (B).
- **Duotap is active form of tapinarof as an antibiotic**
  - Duotap is the active metabolite dimer of tapinarof against MRSA (C) and VRE.
  - Duotap does not give rise to resistance (D).

IP: PCT/US2020/028841



Yale

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YV7045: An accurate, Point-of-Care Diagnostic Test for Respiratory Viral Infections

Principal Investigator: Ellen Foxman, MD, PhD

Background:

- Respiratory viral infections affect millions annually, accounting for a significant portion of global morbidity.
- Current treatment often involves empirical antibiotic use, which contributes to antibiotic resistance.
- The new diagnostic test targets host responses, providing accurate point-of-care results to distinguish viral from bacterial infections.

Indications: Influenza, RSV (Respiratory Syncytial Virus), Common Cold, COVID-19, Bacterial Pneumonia

Innovation & Asset:

- **Host response detection:** Targets immune response instead of pathogen.
- **Rapid diagnostics:** Provides quick results at the point of care.
- **Accuracy:** High precision in distinguishing between viral and bacterial infections.
- **Non-invasive:** Utilizes nasopharyngeal swabs, not blood samples.
- **Ease of use:** Suitable for deployment in any medical provider's office.

IP: US patent: 11,965,218 ; EP patent filed

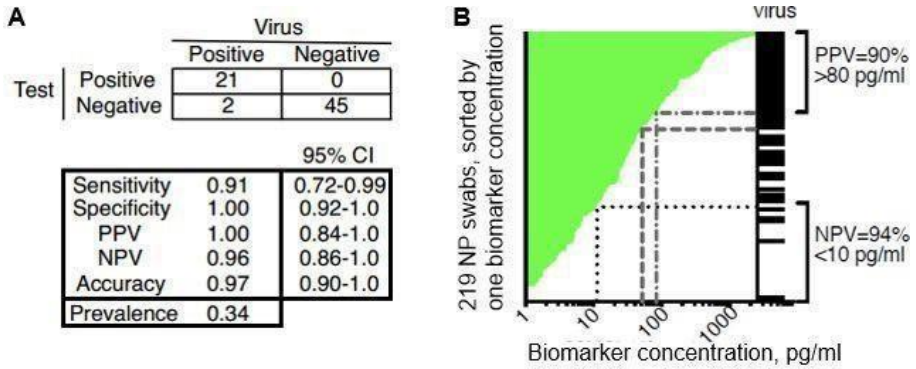

Figure 1: A. Test performance of mRNA biomarker signature. B. Possible rule in/rule out test for viral respiratory infection based on one biomarker protein level, using data from 219 nasopharyngeal swabs.

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YALE VENTURES

YV7021: Protection from Autoimmune Disease

Principal Investigator: Martin Kriegel, MD, PhD

Background:

- Autoimmune diseases like lupus nephritis and autoimmune hepatitis affect millions, causing organ damage and systemic inflammation.
- Current standards include immunosuppressive therapies that often bring significant side effects and limited efficacy.
- The group of Dr. Kriegel at Yale has developed treatment methods to suppress a gram-positive gut commensal species in autoimmune-prone animal models.
- Such protection is achieved against lethal autoimmune clotting leading to heart attacks, lung clots and strokes mirroring antiphospholipid syndrome, liver inflammation as seen in autoimmune hepatitis, and kidney damage due to lupus nephritis in human.
- It is shown that commensal species present in human liver biopsies of autoimmune patients.

Indications: Antiphospholipid syndrome, autoimmune hepatitis, lupus nephritis

Innovation & Asset:

- **Target:** Suppresses gram-positive gut commensals
- **Protection:** Against lethal autoimmune clotting
- **Applications:** Heart attacks, lung clots, strokes
- **Evidence:** Seen in human liver biopsies

IP: US Patent: 11,058,756

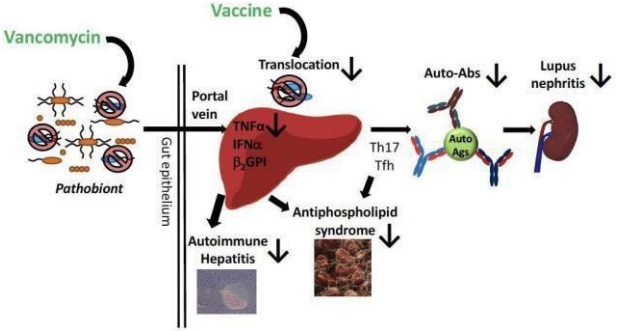

Figure 1. Schematic illustration of the mechanism by which a gut pathobiont promotes autoimmunity and how interventions such as the antibiotic vancomycin or a vaccine against the pathobiont can protect against autoimmune diseases by preventing its translocation of the autoimmune-promoting pathobiont.

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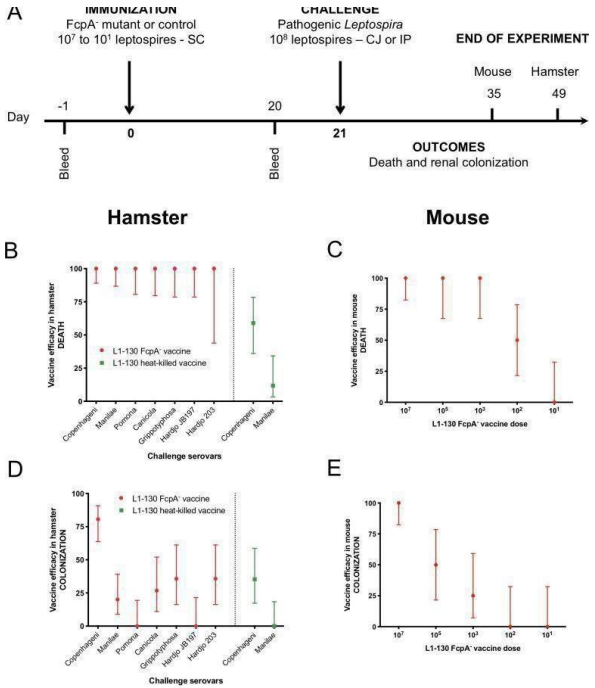
YALE VENTURES

YV6320: Novel Attenuated Live Vaccine for Leptospirosis

Principal Investigator:s Elsio Wunder,PhD, MS, DVM; Albert Ko, M.D.

- Leptospira is a major veterinary pathogen and can cause a life-threatening disease in humans. Although a vaccine is available for animals, it only protects against a few types of the 300 disease-causing *Leptospira* bacteria; it also fails to stop propagating the infection
- We generated a Leptospira strain deficient in flagellar-coiling protein A (FcpA), that provide cross-protective immunity
- Vaccinationwith this strain protects against a lethal challenge with various Leptospira species.
- YV6320 is a safe and efficacious novel vaccine candidate for the treatment of Leptospira infections.
- **Publications:** Wunder *et al*, Mol Microbiol (2016); Elife (2021)
- **IP status:** US10603370B2, issued 03/31/2020
- **Partnered for vet use; Human use still available**



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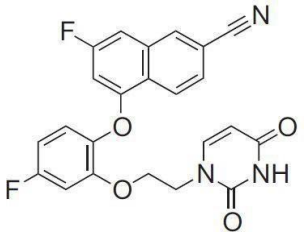
YALE VENTURES

YV6245: In vivo Long-term CR NNRTI

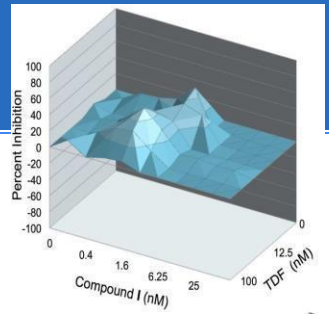
Principal Investigators: William Jorgensen, Karen Anderson, Mark Saltzman

- Marked synergy with current FDA-approved NRTIs (e.g. tenofovir (TDF), INSTIs, and pharma clinical compounds (A) including EFdA(islatravir)
  - Excellent candidate for combination therapyregimens
  - Pre-Exposure Prophylaxis (PrEP)
- Highly soluble with 2-21 nM potency vs. drug-resistant strains, including K101P (e.g., rilpivirine ineffective against K101P) in MT-2 T-cell/HIV-1 assay
- Excellent ADME-Tox and physiological properties (B)
  - No off targets including HERG and CYP3A
  - Excellent in vivo oral bioavailabilityin mice
- Efficacy in humanized AIDS mouse model ©
  - CD4+ ; viral load undetectable
  - Single dose, long-acting (4 week) sustained release nanoparticle formulation
- Efficacy and sustained drug levels in humanized AIDS mouse model for two longacting antiretroviral (LA-ART) formulations
  - an injectable nanoformulation
  - a removable implant delivering the synergistic two drug combination of Compound I and EFdA
- **IP:** issued US patent: 9,382,245



Compound I
EC_{50} = 1.9 nM WT
EC_{50} = 5.6 nM Y181C
EC_{50} = 21 nM Y181C/K103N

A.



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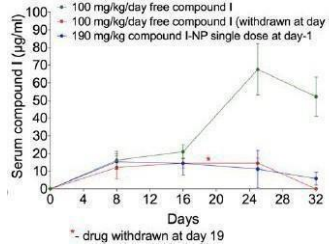
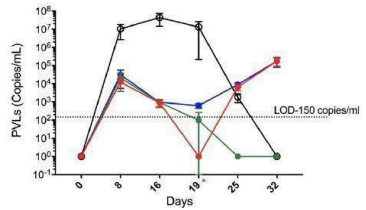


C.



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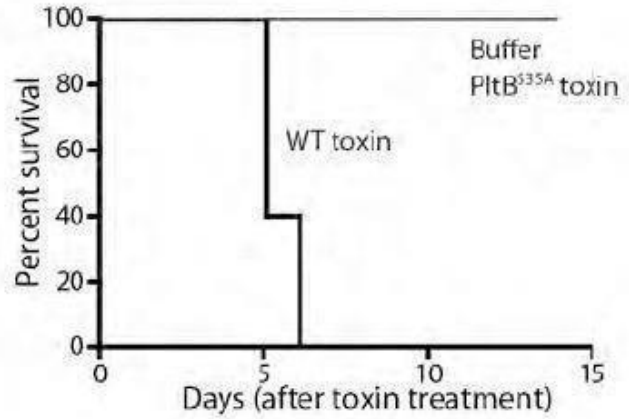
YALE VENTURES

YV6185/6779: Vaccine Candidate for Typhoid Fever

Principal Investigator: Jorge Galán, PhD, DVM

Background:

- Salmonella typhi causes typhoid fever, infecting tens of millions and killing hundreds of thousands of people every year.
- The pathology is mediated by Typhoid toxin.
- Current vaccines show 70-75% effectiveness but have limitations in preventing disease contraction and spread.
- An inactivated version of the toxin can serve as the basis for the development of novel second-generation vaccines to treat typhoid fever.
- In in vivo murine studies, YV6185 conferred full protection against typhoid fever after inoculation with Typhoid toxin, as shown in figure.



Indications: Typhoid fever

Innovation & Asset:

- **Efficacy:** Full protection in murine models
- **Inactivated Toxin:** Basis for new vaccine
- **Mechanism:** Targets Typhoid toxin
- **Reference:** Song et al. (2013) Nature

IP: US patent :10,335,477/10,646,561; EP patent filed

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YALE VENTURES

YV6109: Catalyst-Dependent Synthesis of Glycopeptide Derivatives

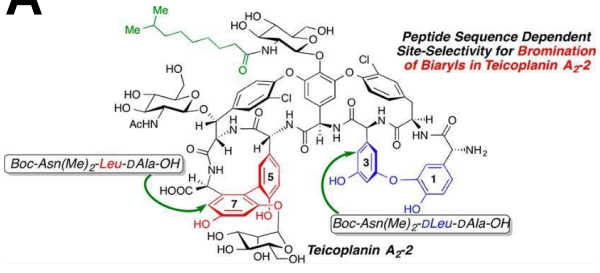
Principal Investigator:

Scott Miller, PhD

Background:

- Glycopeptide analogues may overcome Vancomycin resistance in Staphylococcus & Enterococcus but are difficult to selectively synthesize

A



B

Entry	Compound	MSSA[a,b]	MRSA[c]	VSE[d]	VRE (VanB)[e]	VRE (VanA)[f]
1	Vancomycin	0.5	1	2	16	>64
2	Teicoplanin	0.5	0.5	0.25	0.25	>64
3	Teicoplanin A_2-2	0.5	0.5	0.25	0.25	>64
4	7	0.5	1	0.5	1	>64
5	9	0.5	1	0.25	0.5	>64
6	10	1	1	0.5	1	>64
7	14	2	2	4	8	>64
8	16	0.25	0.25	0.25	0.5	>64
9	20	0.25	0.25	0.12	0.12	32
10	17	0.25	0.25	0.12	0.25	>32
11	18	0.5	0.5	0.25	0.5	>64
12	19	4	2	1	0.5	32
13	21	8	4	0.5	0.25	8
14	22	8	4	0.5	0.25	1
15	Linezolid	4	4	2	2	2

[a]MIC values reported in μg/mL. [b]MSSA = methicillin-susceptible *S. aureus*, ATCC 29213. [c]MRSA = methicillin-resistant *S. aureus*, ATCC 43300. [d]VSE = vancomycin-susceptible enterococci, ATCC 29212. [e]VRE = vancomycin-resistant enterococci, ATCC 51299. [f]MMX 486.

Indications: Novel antibiotic development & compounds

Innovation & Asset: Method of halogenating and cross-coupling glycopeptide antibiotics:

- Demonstrated efficacy using small peptide promoters to selectively brominate the glycopeptide teicoplanin (A)
- Two-step process with yields between 28 - 43%
- Promising minimum inhibitory concentration data from generated compounds (B)

IP: issued US patent: 10,294,27

Novel compounds developed from teicoplanin via selective halogenation with or without cross-linking demonstrate potent activity against five strains of gram-positive cocci. Notably, compounds 21 & 22 (entries 13 and 14) inhibit VanA VRE, which is both vancomycin and teicoplanin resistant.

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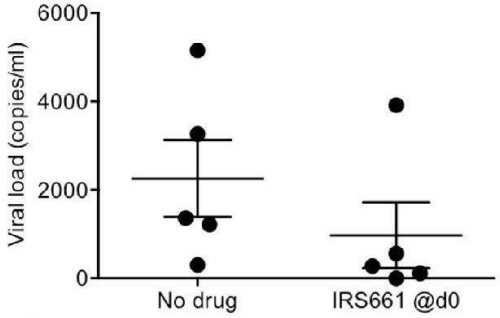
YALE VENTURES

YV6098: TLR-7 Inhibitors reverse virus-induced T-cell anergy

Principal Investigator: David Hafler, M.D.

- Existing antiviral drugs focus on suppressing viral activity rather than awakening the host's immune system;
- chronic infection with RNA viruses such as human immunodeficiency virus type 1 (HIV-1) induces profound dysfunction of CD4(+) T cells
- Activation of the Toll-like receptor 7 (TLR7) on CD4+ T cells results in down-regulation of immune response known as T-cell anergy;
- **Inhibitors of TLR7** reverse T-cell anergy caused by HIV infection, as well as reduce HIV activity in both in vitro and ex vivo systems made of cells from HIV patients;
- In vivo study using a humanized mouse model confirms the efficacy of TLR7 blockade in treating HIV infection; and
- This mechanism opens a new avenue in the fight against chronic infections caused by RNA viruses such as HIV-1



***In vivo* proof of concept using a humanized mouse model.** Viral load measured in mice infected with HIV-1 in the presence (right) or absence (left) of the TLR7 inhibitor IRS661 after 7 days of infection

- **US patent** No 10,308,938, issued 6/4/2019
- **Reference:** Dominguez-Villar, M. *et al.*, Nat. Immunol. 2015

YV5753: Anti-HIV Agents

Principal Investigator: William Jorgensen

Catechol DietherAnalogues as Anti-HIVAgents

- HIV reverse transcriptase (RT) remains a key moleculartarget and a cornerstone for HIV therapy.
- Yale researchers have identified catechol diether derivatives as novel, potent anti-HIV agents.
- These compounds are new non-nucleoside RTinhibitors (NNRTIs) that address continuing issues:
  - concerning the possible emergence of new viral strains
  - improved dosing
  - long-term tolerability
  - safety
- YV5753 is the most potent anti-HIV agent with activity towards wild-type HIV-1; it inhibited replication of HIV-1 in infected human T-cells with an EC50 of 55 picomolar.
- YV5753 is 10 times more potent than any NNRTI reported to date, including the newest FDA-approved drug, rilpivirine.
- Development of the catechol diethers can be expected to yield compounds withhigh therapeutic potential with low toxicity leading to a very high therapeutic index.
- **IP:** issued US patent: 9,487,476

Cellular Therapy, Regeneration & Wound-healing

YV8761: Nav1.7 as chondrocyte regulator and therapeutic target in osteoarthritis

Principal Investigator: Chuan-Ju Liu, Ph.D.

Background:

- Voltage-gated sodium (Na_v) channels essential for the operation of excitable cells, have been found on chondrocytes
- Expression of Na_v1.7, a type of Na_v channel, is increased in chondrocytes from people with osteoarthritis (OA)

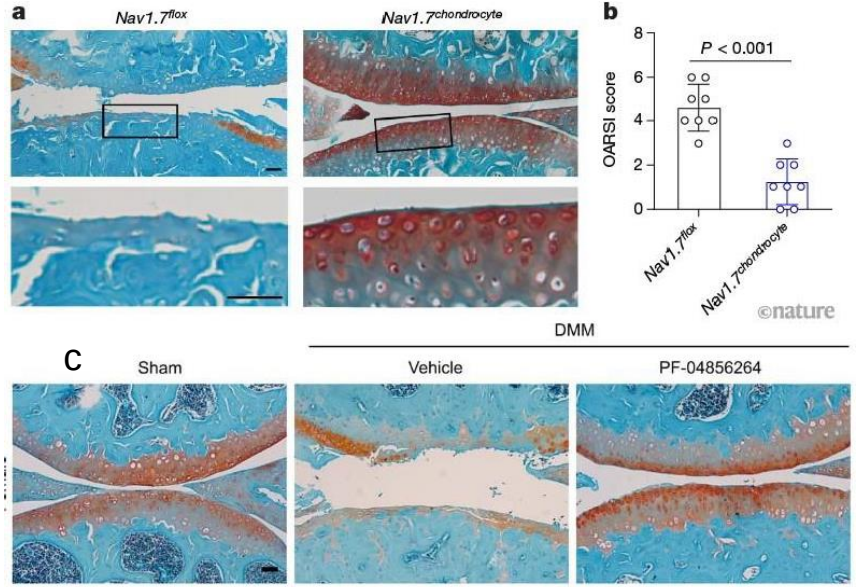
Indications: Osteoarthritis

Innovation & Asset:

- Deletion of the *Nav1.7* gene from chondrocytes protected mice from cartilage loss in chemically and surgically induced-OA
- Treatment with a Na_v1.7-specific blocker or carbamazepine (an approved, non-selective Na_v inhibitor) provide similar chondro-protective effects

Publication: W. Fu, et al., Nature, 2023

IP: Provisional Patent Filed



(a) Representative joint histology 12-weeks post surgical induction of OA. *Nav1.7*$_{flox}$ are control and *Nav1.7*$_{chondrocyte}$ have *Nav1.7* selectively deleted in chondrocytes. Red staining indicates cartilage.
(b) Quantification of the Osteoarthritis Research Society International (OARSI) score.
(c) Representative joint histology from sham and surgically induced OA (DMM). Protective effect of intra-articular administration of PF-04856264 (selective Nav1.7 inhibitor) shown.

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YV8680: CAR-mast cell therapy for solid tumor

Background: Chimeric Antigen Receptor T (CAR-T) cell therapy shows limited efficacy on solid tumors because of T cells' poor infiltration into the tumor tissue, exhaustion and low persistence under an immune-suppressive tumor microenvironment (TME).

Indications: Seeking alternative cell carriers for CAR

Rationales: Mast cells are ideal candidates because 1) they release cytotoxic factors that induce target cell death, (2) they release chemokines and cytokines that recruit T & NK cells into the tumor and remodel TME, (3) they are long-lived (up to years) in tissues and could confer a sustainable anti-tumor effect.

Innovation & Asset: Developing CAR-mast cells for solid tumors

- CAR-Mast cells are specifically activated by tumor antigens.
- CAR-Mast cells release chemokines that attract tumor-infiltrating T and NK cells.
- Direct killing of cancer cells by CAR-mast cells (B)
- Anti-tumor effects by CAR-mast cells in mouse xenograft models (C-D)
- No tissue toxicity or anaphylaxis was observed in the mouse model

IP: Patent application pending

Innovators: Xiaolei Su, PhD

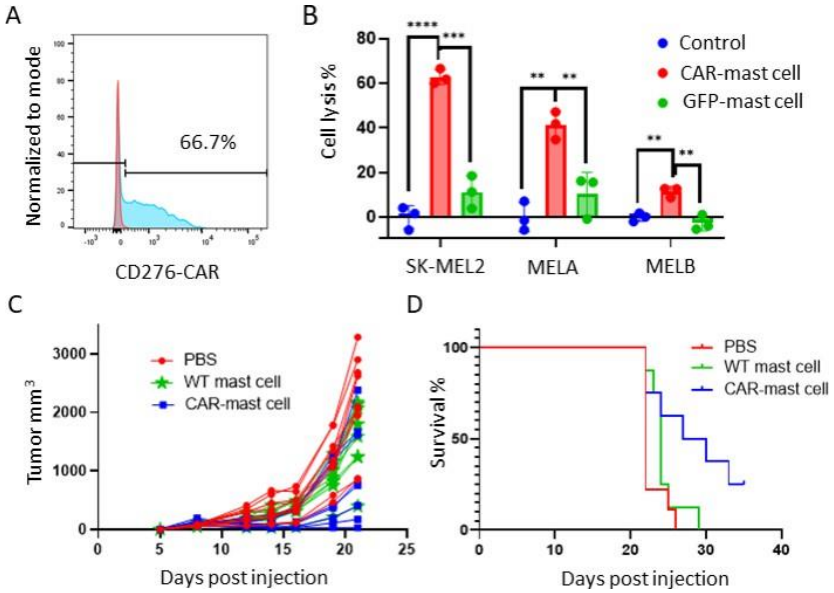

Fig.1 Cytotoxicity of anti-CD276 (B7H3) CAR-mast cells. A) Expression of CD276 CARin mast cells. **B)** CAR-mast cells were incubated with CD276+ human melanoma cells at an E:T= 5:1. **C)** Monitoring tumor growth in C57BL/6 mice xenografted with MC38-CD276+ cells. Each mouse received 5x10^6 MC38 cells at Day0, and 2.5 x10^6 mast cells at Day8 and Day14. **D)** Mice survival following CAR-mast cell treatment.

YALE VENTURES

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Yale

YV8415: Novel peptide to promote neovascularization and wound healing

Principal Investigator: Mehran M. Sadeghi, MD

Background:

- Nearly 10M people in the U.S. have acute or chronic wounds, with chronic wounds presenting a particular and increasing challenge
- The global wound products market is estimated to be ~$15M

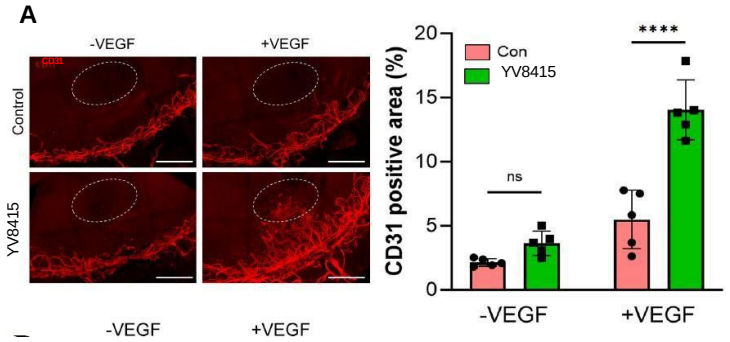
Indications: Wound healing, peripheral arterial disease, critical limb ischemia

Innovation & Asset: Novel Humanized Peptide

- Significantly enhances VEGF signaling, resulting in increased angiogenesis
- Wound healing is significantly accelerated
- YV8415 has the potential to improve outcomes for patients with acute and chronic wounds

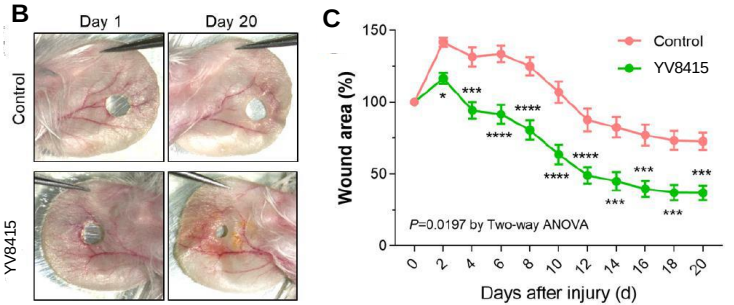
IP: PCT Patent Application Filed

YV8415 Promotes *in vivo* Angiogenesis



(A) Examples and quantification of CD31 whole mount immunostaining (in red) of mouse cornea tissue. The white dashed circles represent the location where the sustained-release pellets were implanted. Scale bar: 500 µm. ****p < 0.0001.

YV8415 Promotes *in vivo* Wound Healing



(B) 2mm diameter circular wounds were made in mouse ears. Typical pictures of wounds in both ears of albino mice on the 1st and 20th days.

(C) Quantification of wound area (n=9).

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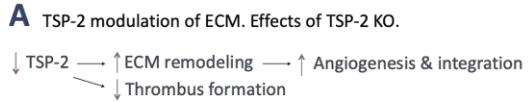
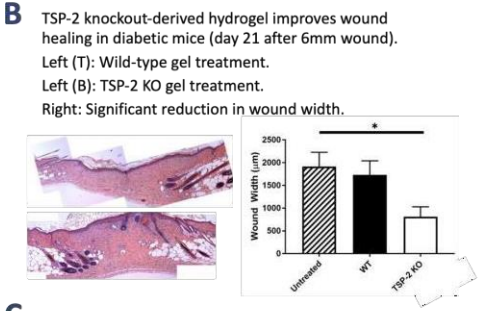
YALE VENTURES

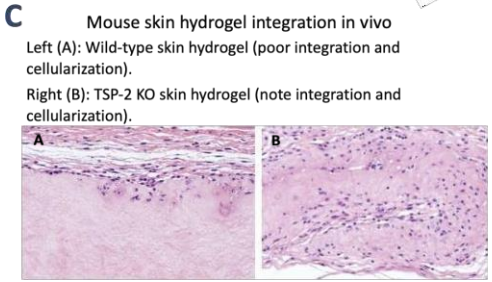
YV8255: Sarxion Biologics, Porcine Decellularized Tissue Platform

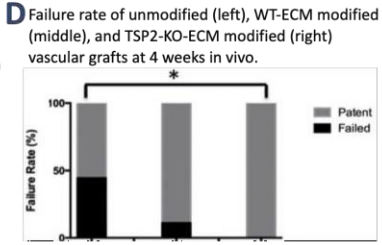
Principal Investigator: Themis Kyriakides, PhD

- **Background:** Current tissue grafts/materials have limited efficacy and duration
  - Many common complications (e.g., dislodging) are caused by poor graft-host tissue integration
  - TSP-2 protein modulates extracellular tissue morphology & compatibility (**A**)
- **Indications:** Hernia patches, wound hydrogels, vascular grafts, plastic surgery, heart valves
- **Innovation & Assets:** TSP-2 knockout animals & their derived, decellularized products
  - Improved wound healing with hydrogel (**B**, **C**)
  - Reduced vasculargraft failure (**D**)
  - TSP2 KO pig skin processing and results (**E**)
- **IP:** US patent filed: 97/159761









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YALE VENTURES

YV7839: Human iPSC-based Tissue Engineered Vascular Graft

PARTNERED

Principal Investigator: Laura Niklason, MD, PhD

Background:

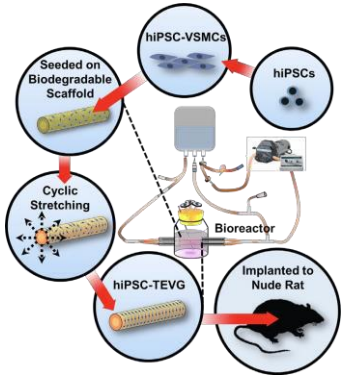
- Tissue engineered vascular grafts (TEVGs) from primary cells face limitations with expandability and donor consistency.
- Current vascular grafts exhibit variable mechanical strength and functional performance.
- New TEVGs developed from hiPSC-derived smooth muscle cells overcome these limitations.

Indications: Vascular grafts, cardiovascular surgeries, coronary artery disease, peripheral artery disease, vascular access for dialysis.

Innovation & Asset:

- **Consistent Quality:** Minimized donor-donor variation using hiPSC-derived cells.
- **Mechanical Strength:** Comparable to clinical saphenous veins.
- **Non-immunogenic:** Reduces rejection risk.
- **Clinical Validation:** Effective mechanical function in animal models.
- **IP:** PCT/US2020/063226

A.

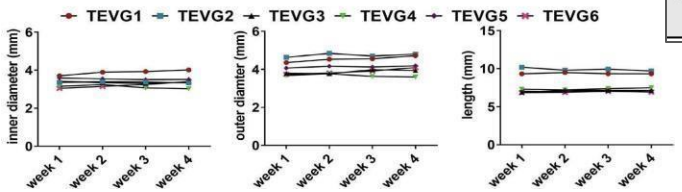


B.

C.

hiPSC-TEVG	
Rupture Pressure	Suture Retention
1419±174 mmHg	158±17 g
Saphenous Vein	
Rupture Pressure	Suture Retention
1599±887 mmHg	196±29 g

D.



A. hiPSC-TEVG generation.
B. Image of hiPSC-TEVG.
C. Mechanical properties of hiPSCTEVGs and saphenous veins.
D. Inner diameters, outer diameters, and length of the implanted hiPSC-TEVGs .

Yale

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YV7416: Novel Topical Peptide Therapeutics and Moisturizers

Principal Investigator: Christopher Bunick, MD, PhD

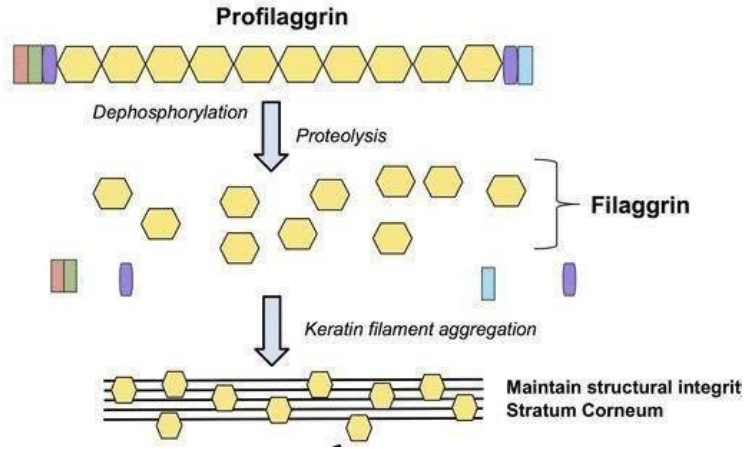
Background:

- Filaggrin truncation mutations cause ichthyosis vulgaris and atopic eczema, affecting skin barrier function.
- Current topical moisturizers focus on lipid replenishment, prevention of water loss, and water absorption, with limited efficacy.
- New technology involves peptide-based agents promoting keratin macrofibril formation, addressing the core issue.

Indications: Atopic dermatitis, ichthyosis, psoriasis, other skin conditions

Innovation & Asset:

- **Targeted Action:** Promotes keratin aggregation for improved skin barrier.
- **Novel Peptides:** Develops short segments crucial for keratin macrofibril formation.
- **Effective Treatment:** Addresses root cause of keratinization disorders.
- **Extended Applications:** Potential basis for new types of skin moisturizers.
- **IP:** US patent filed: 17/283,315



Profilaggrin and filaggrin (FLG) are multi-functional proteins in the maintenance of an optimal skin barrier. FLG monomers specifically bind to keratin (K) intermediate filaments, causing their aggregation into tightly packed macrofibrils and contribute to formation of keratin matrix, which acts as a scaffold for stratum corneum. FLG truncation mutations lead to ichthyosis vulgaris and atopic eczema, two highly common disorders of keratinization.

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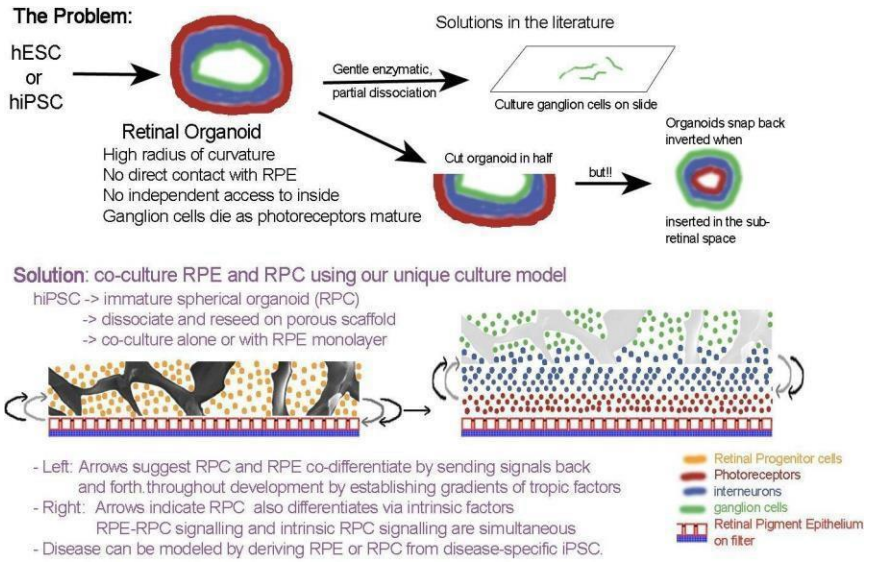
YV7254: Planar Retinal Organoid

Principal Investigator: Lawrence Rizzolo, PhD, FARVO

We developed a biodegradable scaffold for culturing retinal pigment epithelium (RPE) that

- emulate the choroid, (RPE), neurosensory retina, and vitreous in their native anatomical relationship.
- generates laminated retinoids when co-cultured with RPEs Potential applications in treatment (stem cell therapy, implantation) or as a tool in research or drug testing.
- Allows for the study of retinal differentiation, and patient specific mechanisms of retinal disease.
- Emulates both vitreal and eyedrop delivery mechanisms.
- Suitable for patients with mid and late-stage AMD, retinitis pigmentosa (RP), and related diseases.

- **IP status: 17/845,461 pending**
- **Reference:** Biomaterials 2018, 154: 158-168



YV5132: Anti-Aging

Principal Investigator: Laura Niklason, MD, PhD

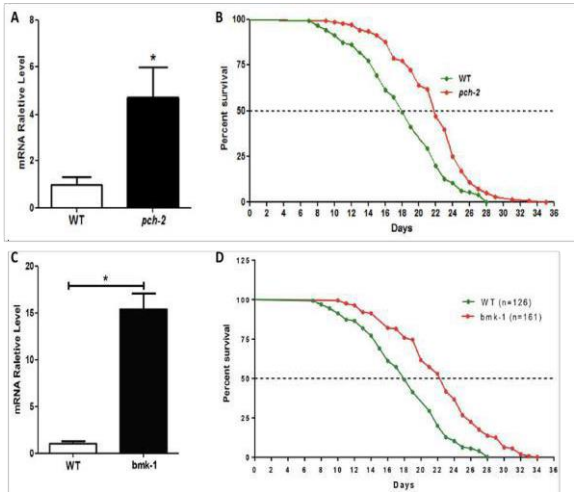
Background:

- Cellular stress contributes to aging and various diseases, impacting over 25% of the population.
- Current anti-aging and stress resistance treatments have limited efficacy and often involve undesired side effects.
- New technology over-expresses specific genes to extend lifespan and enhance stress resistance, solving these limitations.

Indications: Aging, oxidative stress, radiation exposure, DNA damage-induced conditions

Innovation & Asset:

- **Increased Lifespan:** Extends lifespan by ~25% in C. elegans.
- **Stress Resistance:** Enhances survival against oxidative stress, apoptosis, and DNA damage.
- **Human Application:** Confers resistance to environmental stressors in human fibroblasts.
- **Gene Overexpression:** Targets pch-2 and bmk-1 genes for significant impact.
- **IP:** US Patent: 10,772,938
- **Reference:** (1) Qian, H. et al., Aging (Albany NY). 2015 Jan;7(1):1-13; (2) Qian, H. et al., Oncotarget. 2015 Aug 7;6(22):18790-9.



Over-expression of the genes extends lifespan and stressresistance in C. elegans. Gene expression level of (a) pch-2 and (c) bmk-1 and lifespan measurement of (b) pch-2 and (d) bmk-1.

Yale

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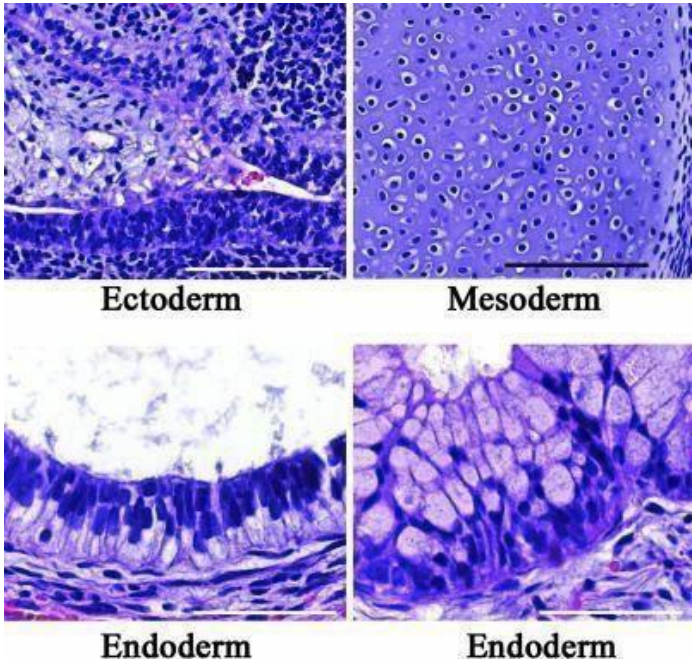
YV4056: Stem Cell Culture Medium

Principal Investigator: Michael Snyder

Animal Product-free Human Stem Cell Culture Medium

- Animal-free product that avoids pathogen or immunogenic contamination of animal products.
- Improved cryoprotection viability to 50-60%.
- Growth as good as or better than the culture which using serum and/or conditional medium.
- Many applications:
  - Differentiate hESC into different tissue/stem/progenitor cells in vitro
  - use as an in vitro model for studying cell proliferation anddifferentiation
  - drug screening platform for cell proliferation, differentiation, and regeneration
  - Produce proteins bytransfection or transduction of DNAor RNA
  - Deliverance of different genes into hESC for research or commercial usage
  - Establish hESC bank with embryo has different genetic background and MHC
  - use as a base for unlimitedsource of cells for therapy

IP: issued US patent: 9,101,590



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Gene Therapy & Genome Engineering

YV8214: Gene Therapy for PKD

Principal Investigator: Michael Caplan, PhD

Background:

- Autosomal Dominant Polycystic Kidney Disease (ADPKD) affects approximately 1 in 1000 people, with 78% of cases caused by mutations in the PKD1 gene encoding the polycystin-1 (PC1) protein
- Current treatment options for ADPKD are limited, and PC1 is too large to be modified through gene therapy strategies
- This technology involves the expression of the C-terminal tail of polycystin-1 (PC1-CTT) to suppress cyst formation and preserve kidney function in ADPKD models.

Indications: PKD

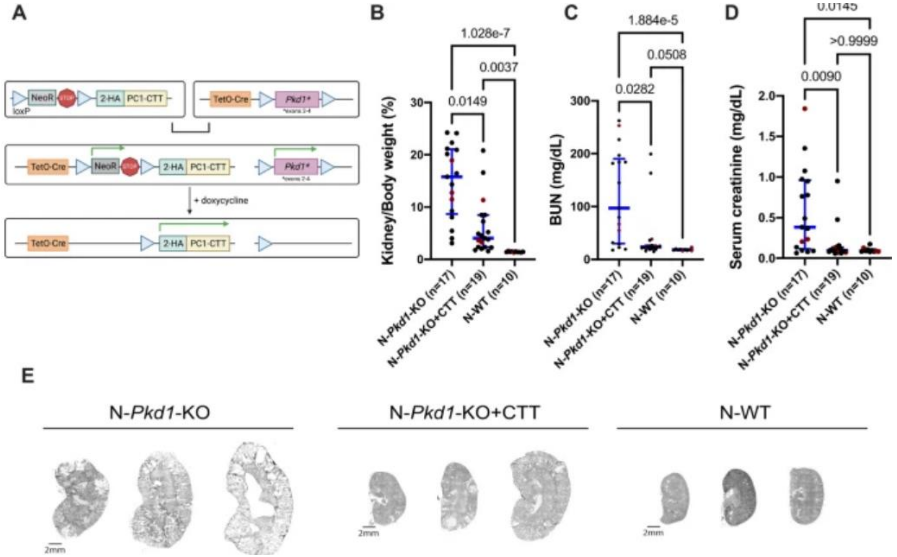
Innovation & Asset:

- **Mitochondrial targeting:** PC1-CTT specifically targets mitochondria, affecting metabolic and redox balance.
- **Gene therapy potential:** Short PC1-CTT fragment could be delivered via gene therapy to suppress cyst growth.
- **Kidney function preservation:** Restores kidney function in ADPKD mouse models, reducing cyst burden.
- **NNT interaction:** Critical interaction between PC1-CTT and NNT necessary for therapeutic efficacy.

IP: U.S./EU Patent Pending

Reference: Onuchik et al. Nat Commun 14, 1790 (2023).

Expression of polycystin-1 C-terminal tail (CTT) suppresses cystic disease in an orthologous mouse model of ADPKD



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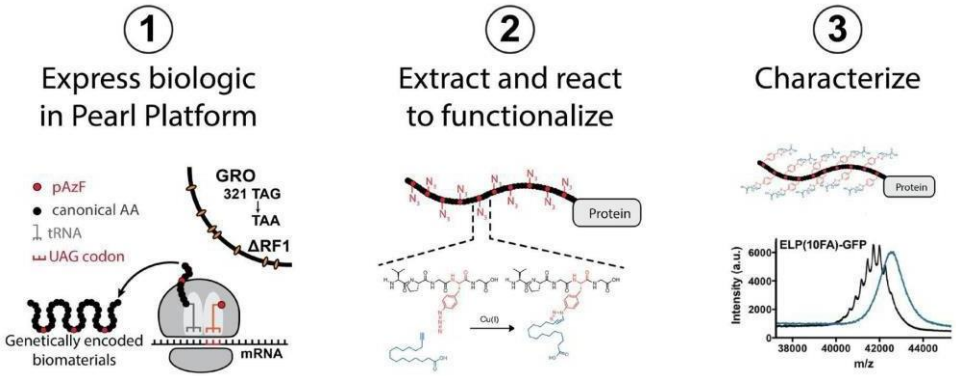
YV: 6349 Precise engineering of protein materials and biologics

PARTNERED

Principal Investigator: Farren Isaacs

- Enable manufacturing of genetically encoded materials (GEMs) for applications in medicine, electronics, environmental sustainability, fabrics, aerospace, and beyond
- Established broad proprietary platform for programmabl GEMs production e
- Advancing proof-of-concept products for technology validation
- Extended protein half-life in an animal model using a GEM that enables site-specific modification with fatty acids
- Created tunable, self-assembling GEM-nanoparticles for applications in drug deliveryand vaccines
- Preliminary in vivo data demonstrates lack of immunogenicityto synthetic amino acids used in GEMs

How it works: specific, multisite modifications to optimize protein properties



Team: Farren Isaacs, PhD, Michael Jew ett, PhD, Natalie Ma, PhD, Barry Schweitzer, PhD

Select Publications: Lajoie et al. Science. 2013;342(6156):357;Amiramet al. Nat. Biotechnol. 2015;33: 272; Orelle et al. Nature. 2015;524(7563):119;Martin et al. Nat. Comm. 2018; 9(1):1203.

YV5714: Protein Engineering

Principal Investigator: Dieter Söll

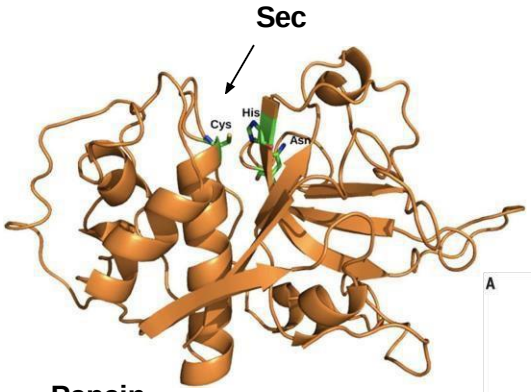
Utility

Selenocysteine (Sec) Method

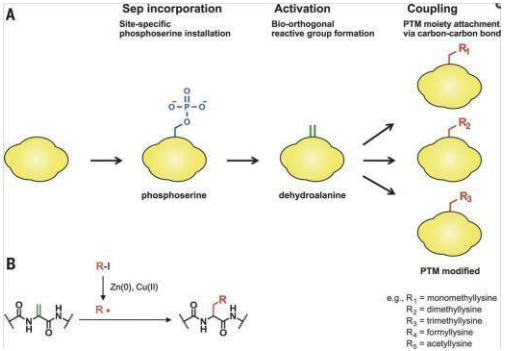
- Industrial Enzymes
- Purified or in vivo
- Cysteine proteases for detergent additives
- Industrial proteins with novel properties
- Rapid Purification
- Efficiencies of incorporation of Sec/U: 70-100%

Phosphoserine (Sep) Method

- Dehydroalanine
- Target for chemical modification of proteins to yield the **natural protein modifications**
- Amenable to “Click Chemistry”
- Issued Patents



Papain



Yang et al (2016) Science 354, 623

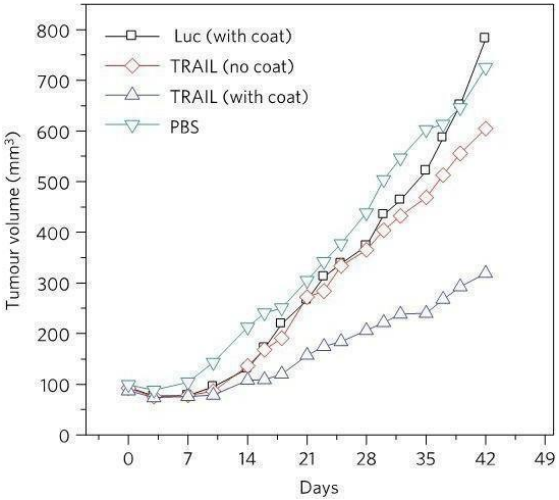
YV4902/5543/6951/6195: Nanoparticles for Controlled Delivery of Nucleic Acids

PARTNERED

Principal Investigator: W. Mark Saltzman, Ph.D.

Nanoparticles for Controlled Delivery of Nucleic Acids

- Numerous formulations for biodegradable nanoparticles for controlled nucleic acid delivery:
  - achieve high loading and encapsulation
  - retain chemical and functional integrity of cargo
- Applications:
  - highly efficient non-viral vectors for DNA/gene delivery;
  - siRNA/mRNA/PNA/oligo delivery for RNA silencing;
  - gene transfection of stem cells;
  - treatment of genetic diseases and cancers, combined gene and drug delivery
- **Pending and Issued Patents:** 9,272,043, PCT/US2015/030169, 14/988,538, others



Tumor size in mice treatedwith nanoparticle-coated TRAIL (proapoptotic gene) w as significantly smaller than that in mice treated withno-coatTRAIL or saline.

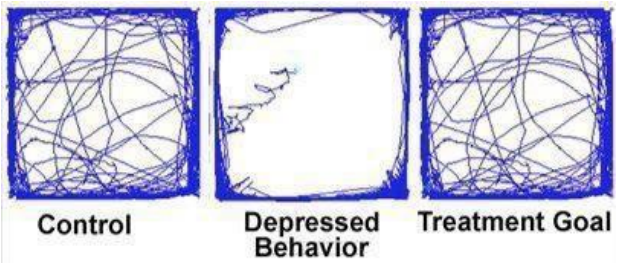
Orphan & Rare Diseases

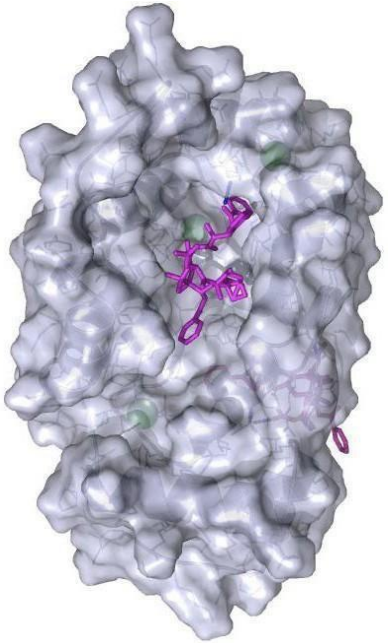
YV7709: Novel Druggable Target for Wolfram Syndrome

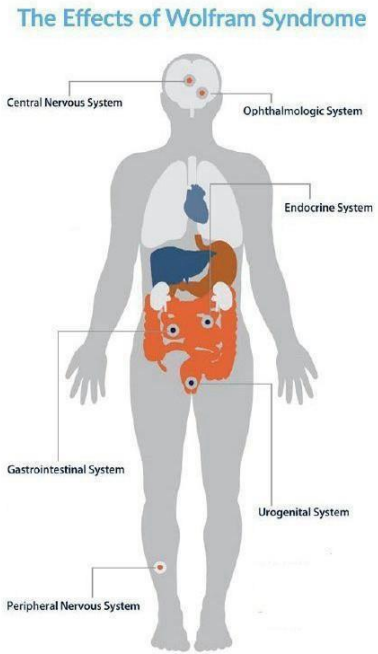
Principal Investigator: Barbara Ehrlich

- Wolfram syndrome = rare genetic disorder
  - Loss of function of gene WFS1
- Homozygous mutation (1 in 770,000 in US)
  - blindness, deafness, mood disorders
- Heterozygous patients
  - 1% of US, 8-fold higher mood disorders
  - No available treatment
  - palliative care only
- Target structures + hits known
- Screenable/Structure-based drug design
- Animal models available for invivo validation

Patent Pending







Yale

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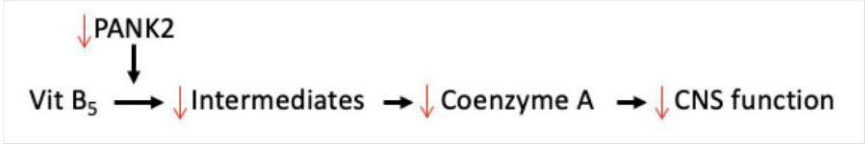
YALE VENTURES

YV7653 & YV7903: PANK3 Activation for Pantothenate Kinase-Associated Neurodegeneration (PKAN)

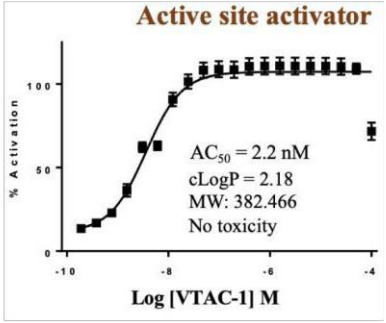
Principal Investigator: Choukri Ben Mamoun, PhD

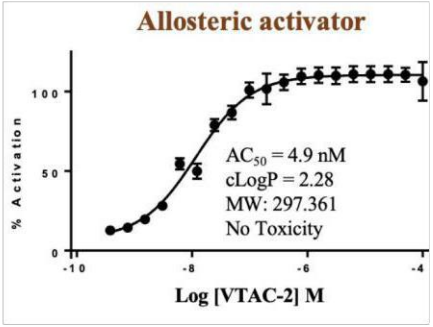
- **Background:** Pantothenate Kinase-Associated Neurodegeneration (PKAN)
  - Neurodegenerative disease caused by autosomal recessive LOF in PANK2 gene (**A**)
  - Estimated 320-1000 patients in USA
  - No disease modifying therapy
- **Innovation & Asset:** Highly potent activators of human PANK3 isoform to rescue CoA synthesis pathway (**B**)
  - 9 lead compounds identified
  - Effective BBB penetration
  - No toxicity in human cell lines
- **IP:** PanK Modulators and Methods Using Same

A PANK2 deficiency leads to defective CoA synthesis, causing progressive neurodegeneration and death.



B Left: VTAC-1 activates human PANK3 via active site.
Right: VTAC-2 activates human PANK3 via allosteric site.





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YV7297: Repair of periodontal disease damage

Principal Investigator: Braddock (Yale); Somerman (NIH NIAMS)

Therapies, Rx Concept & Clinical End-point

- **Disease Outcome:** Loss of cementum tooth loss
- **Examples of current therapies:** Scaling/root planing, surgery , CR
- minocycline-HCL (Arestin®)
- **Unmet Need:** Current approaches do not repair damage predictably (a)
- **Target:** ENPP1 Enzyme (regulates mineralization)
- **Desired Biological Process:** Neocementogenesis
- **Intervention:** Local delivery of ENPP1 antagonist to disease site (b)
  Clinical Endpoint: Reduction in detectable periodontal disease; measurable repair (c)

Current Therapies: Cost and Sales

- **Cost to Treat:** $2K-$30K (visits, treatments, surgery)
- **Sales of Arestin®:** $143M Annual Sales
- **US Patient Population:** 65M Adults

Validity of Therapeutic Hypothesis:

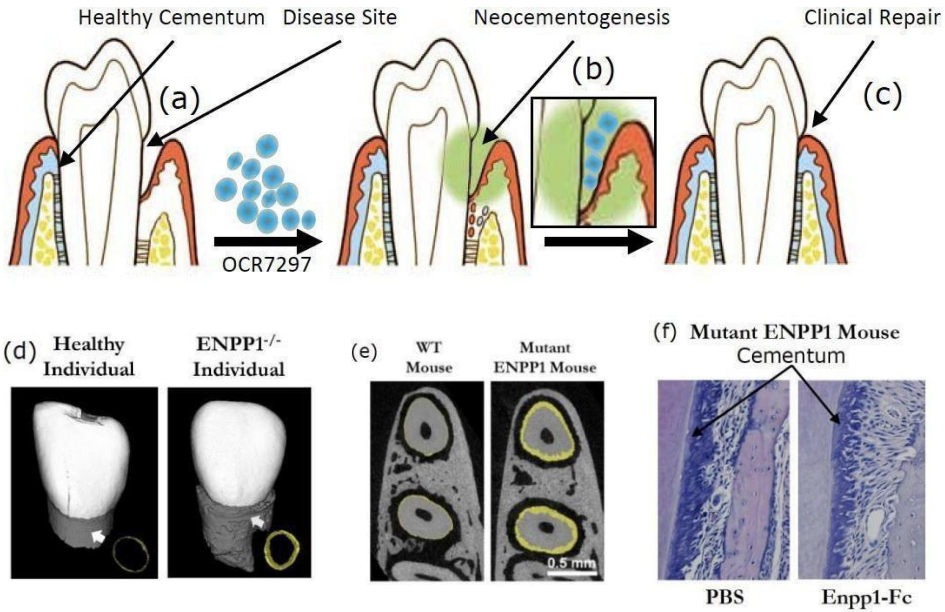
- **Human:** ENPP1 loss Hypercementosis (d)
- **Mouse:** Mutant ENPP1 Hypercementosis (e)
- **Mouse:** Enpp1-Fc reduces cementum (f)

Therapeutic/Regulatory Approach:

- CR small molecule antagonists of ENPP1
- Formulated and delivered as per Arestin®

IP: Patent Pending

Cementum Loss Promotes Periodontal Disease



Yale

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YV6576: Targeting Orphan RASopathy-mediated Cardiac Disease

Principal Investigator: Anton M. Bennett, PhD

Background:

- Aberrant RAS pathway signaling causes cardiac dysfunction and hypertrophic cardiomyopathy (HCM) in infants.

Indications: Cardiomyopathy in Noonan Syndrome (NS) & Noonan Syndrome with Multiple Lentigines (NSML).

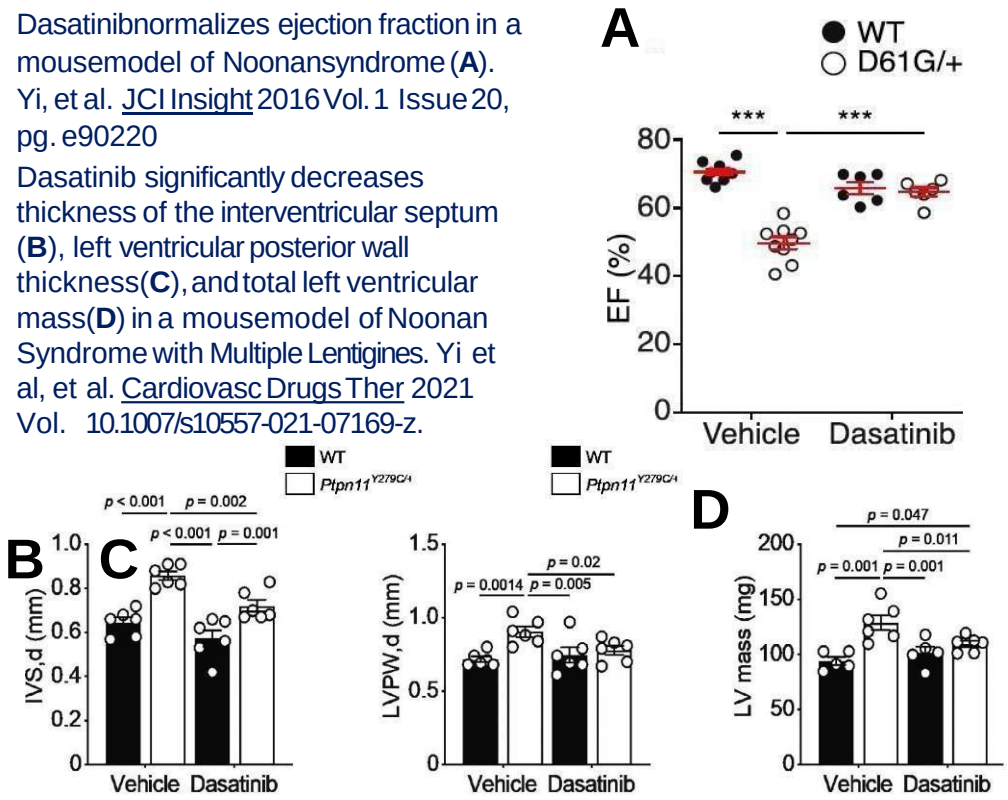
Innovation & Asset: Low-dosetyrosine kinase inhibitor therapy (dasatinib, trametinib).

- Improves cardiac function in mouse models of NS.
- Reduces ventricular and septal wall thickness in mouse models of NS and NSML.
- Potency of cardiac effects at doses 100xbelow chemotherapy dosing.
- Asset class clinically validated.
- Orphan Drug designation granted byFDA for low-dose dasatinib in NS with HCM

IP: Multiple national patents issued; issued US patent: 10,471,059

Dasatinibnormalizes ejection fraction in a mousemodel of Noonansyndrome (**A**). Yi, et al. JCI Insight 2016 Vol. 1 Issue 20, pg. e90220

Dasatinib significantly decreases thickness of the interventricular septum (**B**), left ventricular posterior wall thickness(**C**), and total left ventricular mass(**D**) in a mousemodel of Noonan Syndrome with Multiple Lentigines. Yi et al, et al. Cardiovasc Drugs Ther 2021 Vol. 10.1007/s10557-021-07169-z.



YALE VENTURES

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Yale

YV6436: Treatment for Osteogenesis Imperfecta

Principal Investigator: Chuhan Chung, MD, PhD

Background:

- Osteogenesis Imperfecta (OI) Type VI affects bone mineralization, leading to fractures in early childhood.
- Current treatments have limited effectiveness in restoring bone strength and elasticity.
- New PEDF treatment restores bone elasticity and reduces brittleness in OI models, addressing critical needs.

Indications: Osteogenesis Imperfecta, bone mineralization disorders

Innovation & Asset:

- **PEDF Role:** Regulator of MSC differentiation to osteoblasts.
- **Enhanced Bone Health:** Restores bone elasticity and reduces brittleness.
- **Mechanistic Insight:** Modulates Wnt/β-catenin signaling.
- **Proven Efficacy:** Corrects bone phenotype in animal models (Fig. 1).
- **IP:** US Patent: 10,357,549
- **Reference:** Gattu *et al.* "Determination of mesenchymal stem cell fate by pigment epithelium-derived factor (PEDF) results in increased adiposity and reduced bone mineral content." The FASEB Journal 27.11 (2013): 4384-4394.

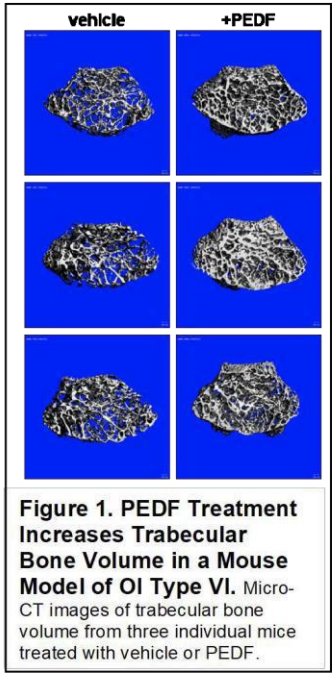

Figure 1. PEDF Treatment Increases Trabecular Bone Volume in a Mouse Model of OI Type VI. Micro-CT images of trabecular bone volume from three individual mice treated with vehicle or PEDF.

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YV5775: Clotting Disorders

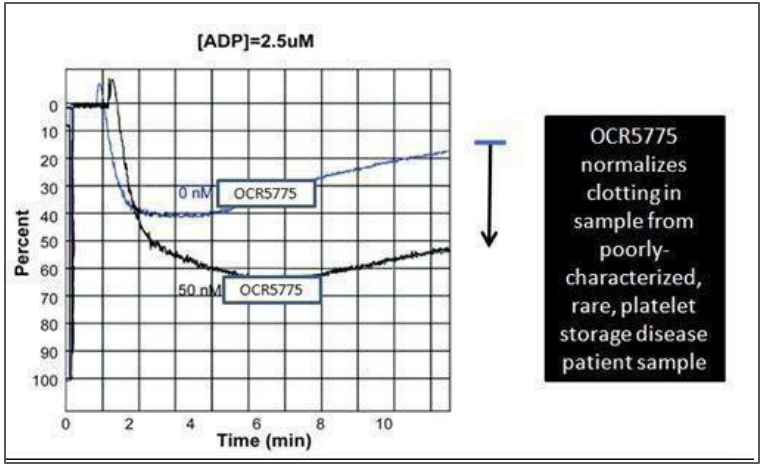
PARTNERED

Principal Investigator: Braddock

Human Serum Enzyme Overcomes Multiple Ultra-Rare Congenital Clotting Disorders

- YV5775 is a therapeutic protein designed to overcome clotting defects:
  - it is resident to the circulatory system
  - has been purified and crystallized to ultra-high resolution
  - its activity is known to be triggered on lyat sites of platelet degranulation triggered under physiological conditions (i.e. response to vascular damage)

- As shown in the figure, weak aggregation is seen in the absence of YV5775 (blue curve) in a patient with a poorly characterized platelet storage disease. The addition of 50 nanomolar of (black curve) normalizes the clotting profile.
- This technology may also have utility in critical care situations, such as in the Emergency Department for acute bleeding episodes (e.g., due to NSAID toxicity), as well as in first-response or military settings.



Several Issued Patents & Reference

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Drug delivery:

Nanoparticles, Topical Technology & Sustained Delivery

YV8728: Sequencing & Targeting of Nucleotide Repeat Expansion RNAs

Principal Investigator: Junjie Guo, PhD

Background:

- Nucleotide Repeat Expansions (NRE) cause 40+ human diseases
- NRE-containing RNAs are difficult to sequence and to selectively target with oligonucleotide drugs

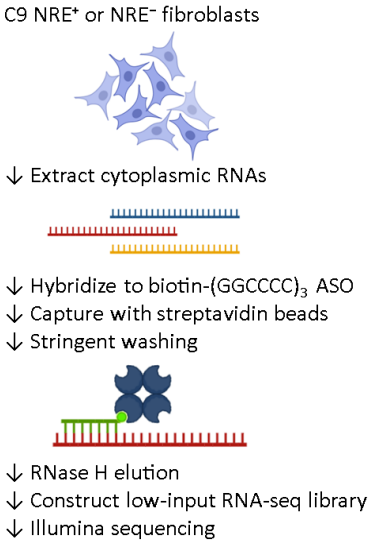
Indications: NRE diseases (primary indication: amyotrophic lateral sclerosis [ALS] & frontotemporal dementia [FTD])

Innovation & Asset:

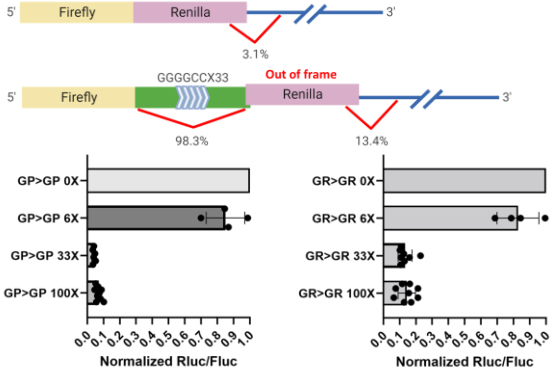
- **Novel method:** General approach for NRE RNA sequencing (A).
- **Aberrant splicing:** Models NRE-induced splicing issues (B).
- **Targeting RNA:** Selectively targets NRE RNAs (C).
- **Proven efficacy:** Effective in targeting (GGGGCC)n repeats in ALS/FTD.

IP: PCT/US2024/034630

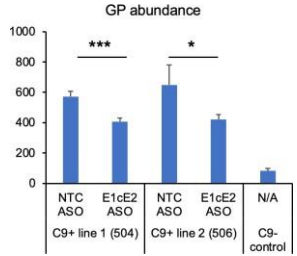
A Novel process of selectively sequencing NRE+ C9orf72 RNA from human fibroblasts



B Assay comparing Firefly to Renilla luciferase effectively models the aberrant splicing induced by NRE at various repeat values.



C In two NRE+ patient fibroblast cell lines, novel antisense oligonucleotide targeted at aberrant splice site successfully reduces levels of the glycine-proline (GP) dipeptide repeat caused by NRE



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YALE VENTURES

YV8475/6265: Anti-guanosine Antibody for Nucleic Acid Delivery

Principal Investigator: James Hansen, MD, MS

Background:

- Viral vectors and synthetic liposomes for gene delivery are limited by complexity of production, limited packaging capacity, and unfavorable immunological features

Indications: Nucleic Acid Delivery for Therapeutics

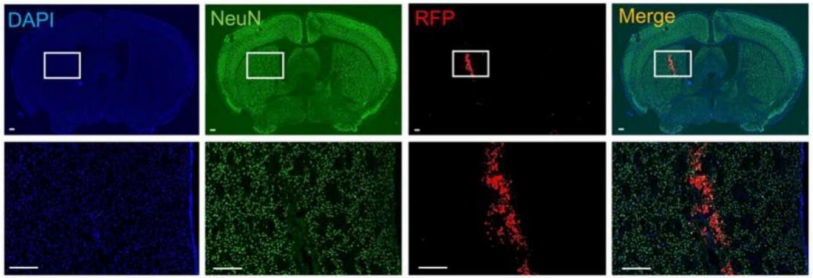
Innovation & Asset: Cytoplasm-localizing anti-Guanosine [or Guanine] antibody, 4H2:

- Binds guanine residues and penetrates cells
- Mediates local mRNA therapy uptake in the CNS (A)
- Delivers mRNA into tumors in vivo (B)

IP: Patent Pending

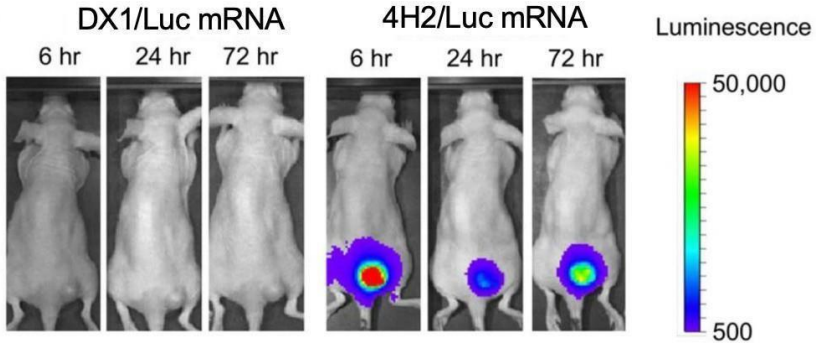
A

4H2/Cre mRNA was injected into the brain of Ai9 Cre reporter mice, and Cre recombinase activity evaluated by RFP fluorescence twenty-four hours later. RFP signal was visualized in the localarea of the injection track.



B

Mice bearing H358 flank tumors received a single intratumoral injection of a mixture of DX1 (similar nucleus-localizing anti-DNA antibody) or 4H2 with Luc mRNA. 4H2/Luc mRNA successfully mediated Luc expression at 6, 24, and 72 hours, while DX1/Luc mRNA did not.



Yale

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YALE VENTURES

YV8181: Nanoparticle-Releasing Vaginal Rings for Intermediate- to Long-term Delivery of Drugs

Principal Investigator: W. Mark Saltzman, PhD

Background:

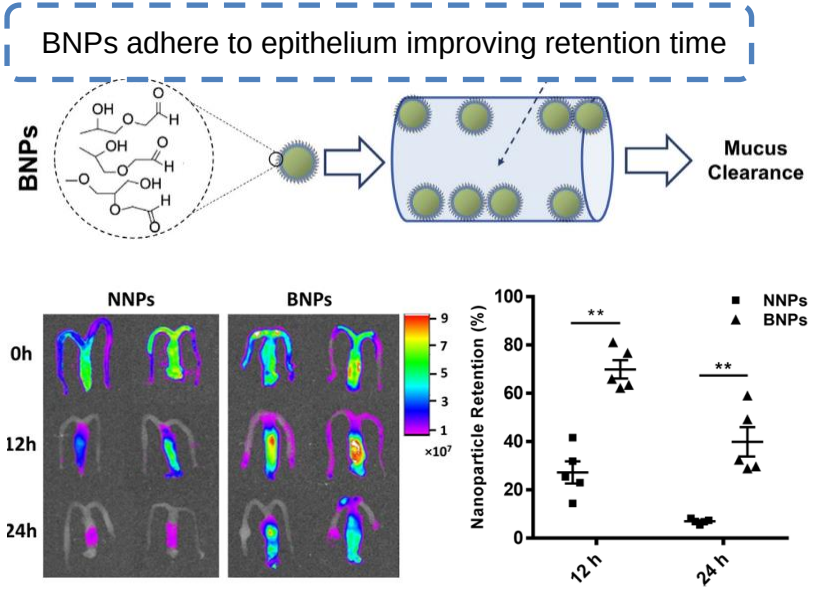
- Cervical cancer and sexually transmitted infections (STIs) affect millions of women worldwide. Current treatments often fail to offer sustained local drug delivery.
- Existing vaginal drug delivery systems lack effective long-term retention due to mucosal shedding and frequent mucus secretion.
- **This** novel nanoparticle (NP) and intravaginal ring (IVR) technology improves drug distribution, retention, and prolonged delivery.

Indications: Cervical cancer, STI prevention, vaginal vaccines, contraceptive delivery

Innovation & Asset:

- **Sheddable-PEG NPs:** Innovative NP system transforms from a non-adhesive to adhesive form.
- **Enhanced retention:** NPs adhere to vaginal epithelium, improving retention and efficacy.
- **Sustained release:** Overcomes mucosal shedding for prolonged drug delivery.
- **Versatile application:** Suitable for multiple drug types, including vaccines and antiviral agents

IP: PCT/US2023/018528



BNPs greatly enhance retention and distribution of nanoparticles in the vaginal lumen over NNPs

Yale

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YALE VENTURES

YV7861: DNA-brick assisted liposome sorting

Principal Investigator: Chenxiang Lin, PhD

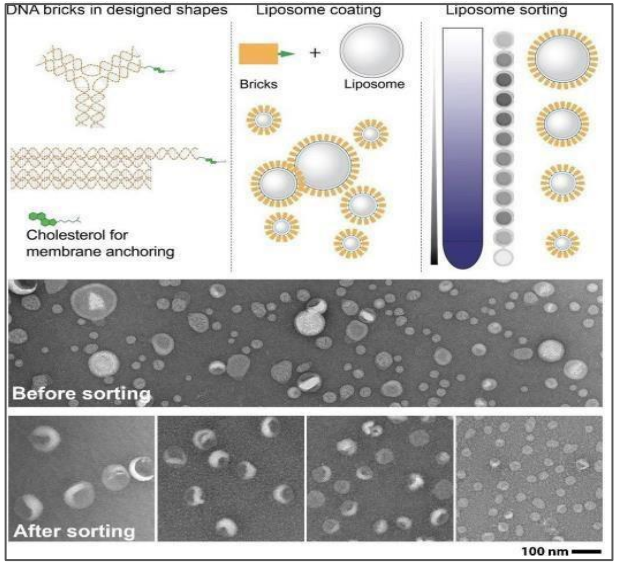
Background:

- Size-controlled liposomes are crucial for research and biotechnology, yet current methods lack precision and scalability.
- Traditional homogenization techniques show limitations in achieving uniformity and retaining cargo functionality.
- New DNA-brick assisted density-gradient centrifugation sorts heterogeneous liposomes effectively, solving these issues.

Indications: Membrane biophysics studies, liposomal drug delivery, biotechnology applications

Innovation & Asset:

- **Precise Sorting:** Achieves uniformly-sized liposomes.
- **Cargo Integrity:** Retains protein and nucleic-acid functionality.
- **Versatile Application:** Effective for various liposome sizes and contents.
- **Research Utility:** Enhances membrane biophysics studies.
- **IP:** US Patent: 11,951,211
- **Reference:** BioRxiv (2020.02.01.930321v1)



Top: the process of DNA-brickassisted liposome sorting. Bottom: TEM images of a pool of heterogeneous liposomes before sorting and the uniformly- sized liposomes after sorting.

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YALE VENTURES

YV7119: Nanomaterial technology to enable efficient oral drug delivery

PARTNERED

Principal Investigator: Jiangbing Zhou, Ph.D.

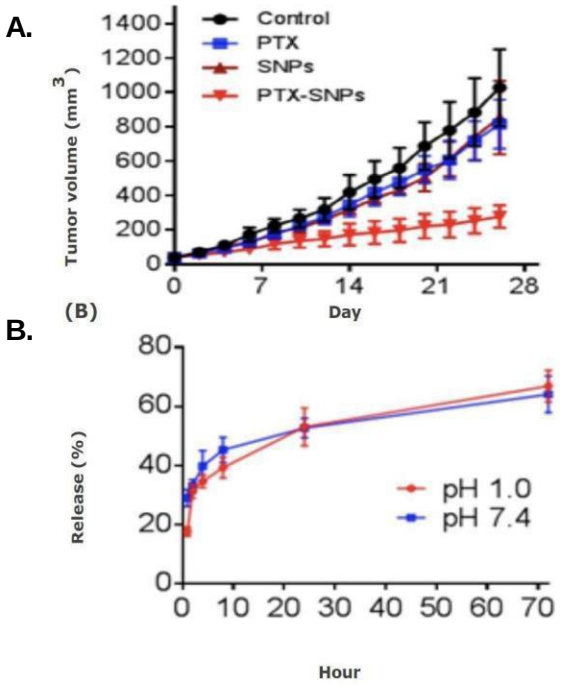
Background:

- Enhancing oral bioavailability of drugs, especially chemotherapeutic and peptide therapeutics, is a significant challenge.
- Current drug delivery methods struggle with stability in acidic environments and effective gastrointestinal penetration.
- New supramolecular nanoparticles (SNPs) enhance drug stability and absorption, addressing these challenges effectively.

Indications: Tumors, diabetes, stroke

Innovation & Asset:

- **Enhanced Bioavailability:** SNPs significantly improve oral drug bioavailability.
- **Acid Stability:** Stable in strong acidic environments (as low as pH 1.0).
- **Effective Penetration:** Efficient gastrointestinal tract penetration.
- **High Efficacy:** Improved plasma concentration and tissue adsorption.
- **IP:** US Patent: 11,478,433.



Enhanced bioavailability and stability of orally delivered drugs. (A) Oral administrated drug paclitaxel (PTX)-SNPs reduced tumor volumes substantially compared to control group, free PTX, and empty SNPs. **(B)** Exposure to pH 1.0 did not change the release of PTX from SNPs.

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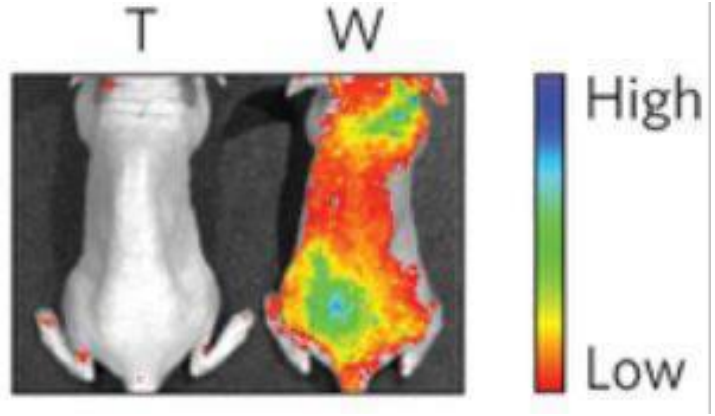
YV6839/6688: Adhesive, Non-absorbent Nanoparticles for Dermal Applications

PARTNERED

Principal Investigator: Mark Saltzman, Ph.D., Michael Girardi MD

- Biodegradable nanoparticles that stick to skin, are removed by friction, but don't wash off
- Demonstrated efficacy using sunblock in rodent models
- Prevents UV damage to skin
- Wipes off with towel, doesn't wash off with water
- Many possible non-prescription and prescription applications
- Clinical trial of sunblock currently enrolling subjects
- **Reference:** Deng et al. (2015). Nature Materials
- **IP status: pending applications:** US15/573,807, EP16727876.1, HK18112243



BNPs encapsulating an infrared dye, **IR-780**, were applied to the dorsal skin of mice. After wiping with a wet towel (T) or washing with water (W), their skin retention was imaged withXenogen. Deng et al. (2015). Nature Materials

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YV6785: Nanoparticles to Target the Pancreas

PARTNERED

Principal Investigator: Tarek Fahmy, Ph.D.

Polymeric Bile Acid Formulations for Targeted Delivery

- A new class of polymer biomaterials (PUDCA) that are selectively taken up and retained in the pancreatic, hepatic and colon microenvironment.
- Formulated as orally administered, safe and biodegradable nanoparticles.
- Unique properties: encapsulates drugs and/or agents, pH-responsive, enables sustained release.
- **Indications:** targeted delivery of drugs and tracking/imaging agents to sites of pancreatic, hepatic and colonic inflammation. For therapy and diagnostic uses
- **IP status:** PCT/US Application filed 62/214,648
- **Publications:** Unpublished work

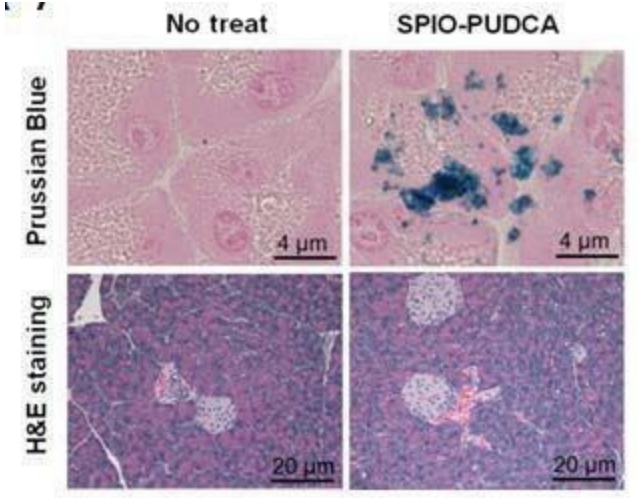

FIG. Histologyimages of pancreatic sections from mice that were orally treated with PBS or PUDCAnanoparticles containing iron oxide (SPIO-PUDCA). Iron Oxide is assayed using the Prussian Blue stain which appears distinct in the pancreas.

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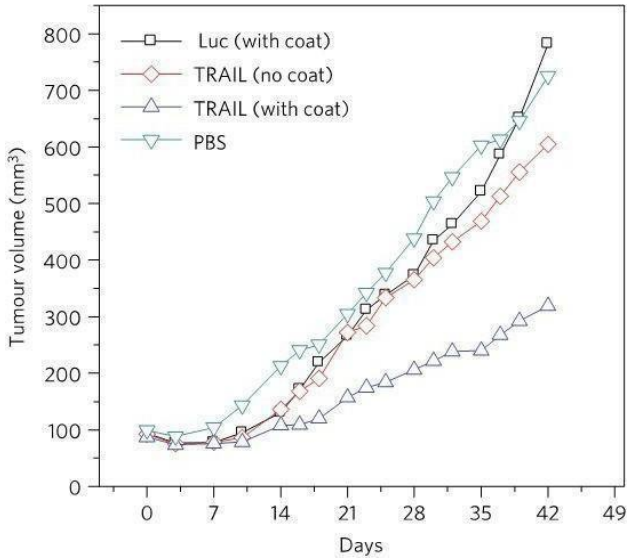
YV4902/5543/6951/6195: Nanoparticles for Controlled Delivery of Nucleic Acids

PARTNERED

Principal Investigator: W. Mark Saltzman, Ph.D.

Nanoparticles for Controlled Delivery of Nucleic Acids

- Numerous formulations for biodegradable nanoparticles for controlled nucleic acid delivery:
  - achieve high loading and encapsulation
  - retain chemical and functional integrity of cargo
- Applications:
  - highly efficient non-viral vectors for DNA/gene delivery;
  - siRNA/mRNA/PNA/oligo delivery for RNA silencing;
  - gene transfection of stem cells;
  - treatment of genetic diseases and cancers, combined gene and drug delivery
- **Pending and Issued Patents:** 9,272,043, PCT/US2015/030169, 14/988,538, others



Tumor size in mice treated with nanoparticle-coated TRAIL (pro- apoptotic gene) was significantly smaller than that in mice treated with no-coat TRAIL or saline.

Diagnostics/ Biomarkers/Imaging

YV8907: Tracers for Imaging Collagen Turnover

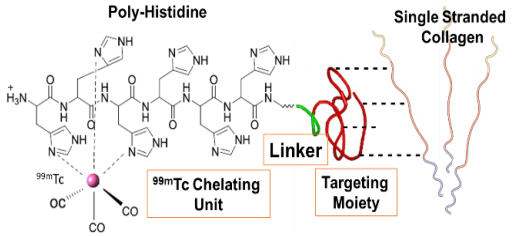
Principal Investigator: Mehran M. Sadeghi, MD

Background:

- Fibrosis is a common pathologic process, but current imaging techniques provide only static images of tissue structure without information about active fibrogenesis

Indications: Cardiac fibrosis imaging (primary) & other fibrosis-related diseases

A



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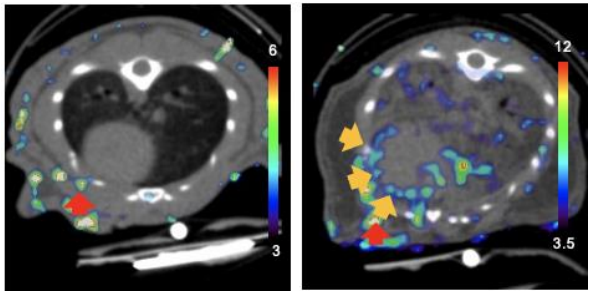

Examples of SPECT/CT images acquired at 2 hours post injection of ^{99m}Tc-His6-$(GPO)_9$ in mice at 5 days after LAD occlusion (right) and sham operation (left) demonstrating uptake of the tracer in the anterior and lateral myocardium (orange arrows). Cutaneous uptake, probably related to surgery, is observed in both animals (red arrows).

Innovation & Asset: Novel ^{99m}Tc-His6-$(Glycine\text{-}Proline\text{-}Hydroxylysine)_9$ radiotracer:

- Uniquely targets single-stranded collagen and contains adjustable linker to modulate hepatic/renal clearance rates (A)
- Readily-detectable in vivo signal after myocardial infarction (B) and transverse aortic constriction (data not shown)

IP: US Patent Pending (PCT: WO 2022272268)

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YV8478/YV8790: Troplex™ for Optimal Sequencing of ADC Intervention for Breast Cancer Patients – CAP/CLIA Approved

Principal Investigator: David Rimm, MD, PhD

Background:

- ADCs are very promising therapies for metastatic breast cancer and other tumor types that express the ADC target (e.g.,Trastuzumab Deruxtecan for HER2+ and Sacituzumab Govitecan for TROP2+).
- Sequencing ADC therapeutic options directly impacts patient outcomes[1] .
- Troplex™ provides quantitative analysis of HER2 and TROP2 and percentile rank to inform therapy sequencing by clinicians.

Innovation & Asset:

- **Dual biomarker assessment:** CLIA validated assay quantifies HER2 and TROP2 in tumor tissue.
- **Treatment guidance:** Identifies dominant biomarker for optimized ADC therapeutic sequencing.
- **Personalized oncology:** ADC sequencing Improves patient outcomes[1].
- **How it aids physicians:** Adaptable reporting with percentile comparisons for each biomarker.
- **Reimbursable**: TBD - but planning 88346/88350/88361

IP: Patent application filed.

Learn More: Visit Yale Pathology Labs - Troplex Assay

HR+/HER2-Low Efficacy Data (n=56)

SG → T-DXd (n=24, 42.9%)

- Median lines of therapy for MBC prior to SG:
  - Median lines chemotherapy: 2.0 (range 0-5)
  - Median total lines of therapy: 3.0 (range 0-9)
- Intervening therapies between ADCs: 47.8%

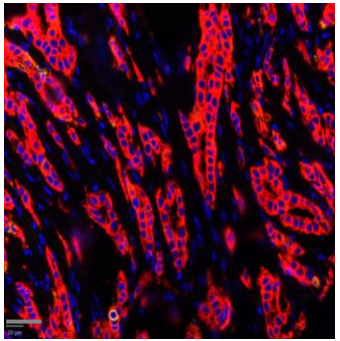
	ADC1 (SG)	ADC2 (T-DXd)
ORR (CR+PR) by investigator assessment, %	77.3%	34.8%
CBR (CR + PR + SD) by investigator assessment, %	86.4%	60.9%
Median rwPFS, months	8.0	3.7
Median rwOS from time of each ADC start, months	22.8	7.8

T-DXd → SG (n=32, 57.1%)

- Median lines of therapy for MBC prior to T-DXd:
  - Median lines chemotherapy: 2.0 (range 0-5)
  - Median total lines of therapy: 4.5 (range 2-10)
- Intervening therapies between ADCs: 42.4%

	ADC1 (T-DXd)	ADC2 (SG)
ORR (CR+PR) by investigator assessment, %	46.9%	18.5%
CBR (CR + PR + SD) by investigator assessment, %	78.1%	37.0%
Median rwPFS, months	5.5	2.6
Median rwOS from time of each ADC start, months	19.8	10.1

SG as ADC1 demonstrates better rwOS outcomes, with similar rwPFS for both ADCs as first-line treatments. Sequence significantly impacts efficacy, particularly for rwOS, underscoring the importance of treatment order in real-world settings.



Troplex™ provides quantitative ADC antigen analysis of HER2 and TROP2 expression in breast cancer tissues.

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[1]Drago, J., Modi, S. Expanding the use of T-DXd in metastatic HR-positive breast cancer: where are we now?. *Nat Rev Clin Oncol* (2024). https://doi.org/10.1038/s41571-024-00963-2

YV7177: Imaging Acceleration Methods For MRI Parameter Mapping

Principal Investigator: Dana Peters, Ph.D.; Chenxi Hu, Ph.D.

SUPER: A Novel Acquisition and Reconstruction Strategy For Improved Efficiency and Resolution in MRI Parameter Mapping

- There have been many approaches to accelerate parameter mapping, such as parallel imaging, MR fingerprinting, compressed sensing, etc.
- Here we propose a novel acquisition and reconstruction strategy for accelerating parameter mapping, called SUPER for “Shift Undersampling improves Parameter mapping efficiency and Resolution”.
- This technique is especially suitable for applications where multiple TIs or TEs are needed and can improve either resolution or acquisition time. It can be applied

  to the following: edema imaging, myocardial infarction and fibrosis, iron overload in heart and liver, water-fat separation (Dixon methods), clinical neural imaging, functional MRI, solid tumor imaging. We demonstrate this technique in

  Figures 1 and 2 in vivo MOLLI, which is the standard cardiac T1 mapping method
- **IP status:** Provisional Patent Application No. 62/481,361
  Reference: unpublished work

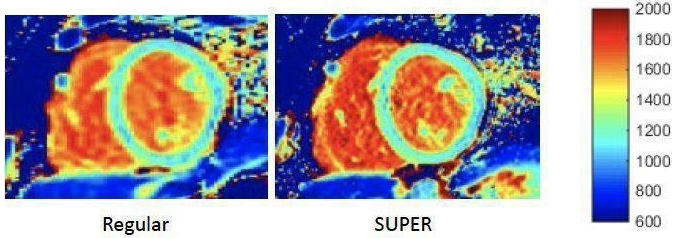

Figure 1: Image comparison: the same time is used, the image resolution doubles

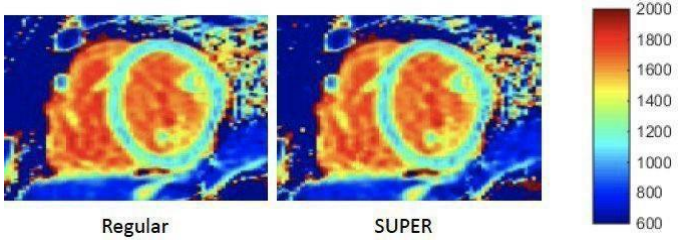

Figure 2. Image comparison: time is reduced un SUPER, while image quality is retained

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YALE VENTURES

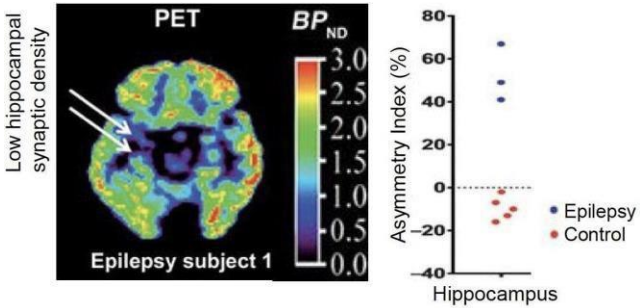
YV7160: Radiopharmaceuticals for synaptic imaging

Principal Investigator: Zhengxin Cai, PhD

Fluorine-18 labeled radiopharmaceuticals for synaptic vesicle glycoprotein 2A (SV2A) imaging and their use as biomarkers for synaptic density

- Many neurological and psychiatric diseases, such as Alzheimer's and Epilepsy, are characterized by misfiring synapses.
- Currently, there is no way to visualize healthy or aberrant neuronal connections in the living human brain.
- SV2A radioligands combined with positron emission tomography (PET) can be used to noninvasively quantify synaptic density in the living human brain.
- Fluorine-18 labeled SV2A radioligands have a longer half-life (110 min) making them suitable for commercialization and clinical applications.
- This promising method enables routine brain monitoring in patients with neurological diseases, where synaptic loss or dynamic changes in density could provide clues to prognosis.
- **Reference:** Finnema et al. (2016) Science
- **IP status:** EP and US Patents issued (US11,518,754)

PET evaluation with SV2A radioligand reveals unilateral sclerosis in epilepsy patients.



(Left)The white arrows indicate loss of SV2A radioligand binding in the mesial temporal lobe. (Right) Asymmetry indices between left and right hemispheres for healthy control subjects and between ipsilateral and contralateral hemispheres for epilepsy patients. Data are individual subjects

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YV6966: MMP-associated Inhibitors and Tracers

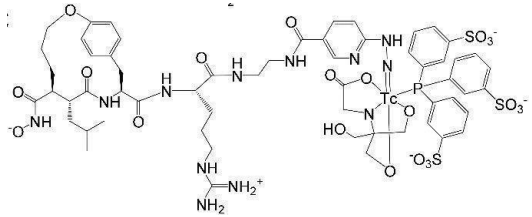
Principal Investigator: Mehran Sadeghi

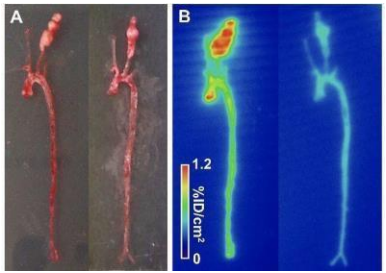
Novel matrix metalloproteinases (MMPs) Inhibitor and MMP-targeted imaging tracers

- Upregulationof MMPs is associated witha wide range of diseases including cancers, inflammation and cardiovascular diseases.
- Measurement of MMPexpressionand activation in vivo could enable physicians to accurately diagnose and treat MMP-associated diseases.
- Currently there are no tracers available in the clinic for imagingMMP activity.
- A new type of a MMP inhibitor (1) has been developed, whichalsoserves as a versatile scaffold (3) for developing MMP-targeted imaging agents.
- Additionally, a novel precursor was also designedas a parent building block for making different type of hydrophilic MMPimaging tracers.
- Thesenovel scaffolds display improved pharmacokinetics and water solubility as compared to previously reported MMPSEPCT probes (i.e.RP805)

IP: issued US patent: 11,286,251

Novel MMP inhibitor and MMP-targeted imaging tracer 99mTc-RY M1





99mTc-RYM1 imaging of carotid aneurysm
Ex-v iv o photography (A) and autoradiography (B) of aortae and carotid arteries f rom apoE-/- mice with CaCl2-induced carotid aneurysm injected with 99mTc-RY M1 without (left) and with the pre-injection of an excess of MMP inhibitor, RYM (right).

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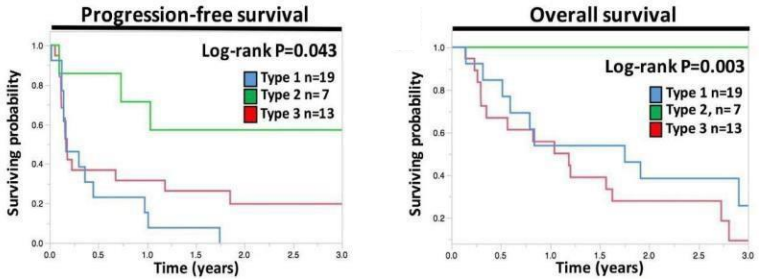
YV6922: Selection of Non-Small Cell Lung Cancer Patients Responsive to Checkpoint Inhibitors

Principal Investigators: Kurt Schalper & David Rimm

- Quantitative Immunofluorescence was used to examine Tumor- Infiltrating Lymphocytes (TIL) in pretreatment NSCLC tumor samples.
- TIL levels of CD3, Granzyme B and Ki67 revealed a dormant phenotype of TIL's in pretreatment tumor samples that correlated with clinical response to Checkpoint Inhibitor therapy.
- Patients with tumors displaying a combination of high CD3, low Granzyme B and low Ki67 levels displayed the best response to Checkpoint Therapy.
- Early evaluation of NSCLC tumors with this method may select patients most likely to benefit from these Therapies.

IP: issued US patent: 11,644,467



Kaplan-Meier graphical analysis of 3-year progression free survival and overall survival of lung cancer cases treated with immune checkpoint blockers according to their TIL phenotype panel:
Type 1: Low CD3
Type 2: High CD3 + Low Granzyme B + Low Ki67
Type 3: High CD3 + High Granzyme B OR High Ki67

The number of cases in each group and the log-rank P value is indicated in the chart.

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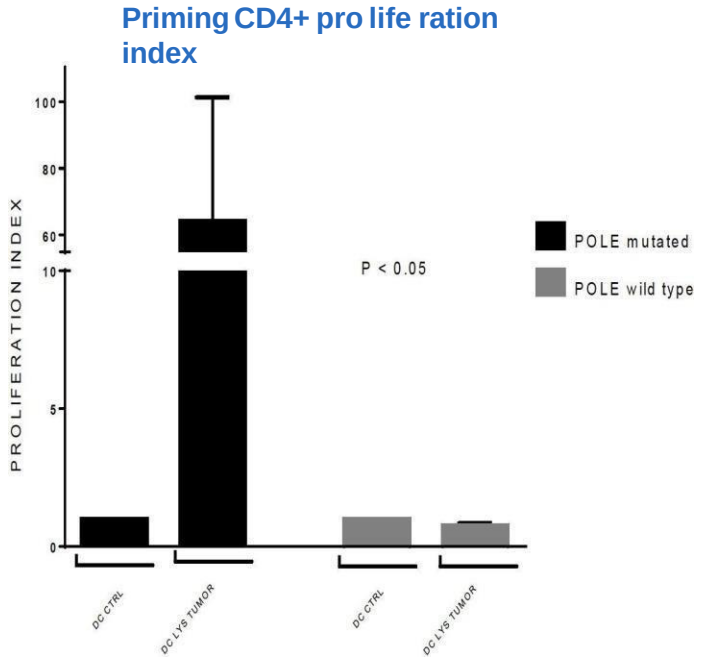
YALE VENTURES

YV6104: Tumor Biomarker for Prognosis of Response to Immunotherapy

Principal Investigator: Alessandro Santin

- Whole-exome sequencing of tumor samples identified a subset of tumors with a disproportionately large number of somatic mutations.
- This hypermutator phenotype is due to somatic mutation in DNA Polymerase epsilon (PolE).
- Tumors with this phenotype and PolE mutation are highly immunogenic (see figure).
- Sequencing of tumor PolE for somatic mutation is an efficient way to select patients who will best respond to immunotherapy.
- A US patent application has been issued (US 11,098,367).



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YV5151: Biomarkers for Neonatal Sepsis

Novel Biomarkers for Detection of Early Onset Neonatal Sepsis

- Infection-induced preterm birth significantly raises the risk of the newborn developing early onset neonatal sepsis (EONS) and represents a significant contributor to morbidity and mortality worldwide.
- Premature newborns represent about 11% of the approximately 4 million live births in the US annually and are most susceptible to developing EONS.
- The standard of care is empiric antibiotic therapy based upon minimal symptomatic suspicions, but this poses undue risks to the newborn.
- Using proteomic analyses, Yale researchers have identified biomarkers in cord blood samples that correlate with the development of EONS.
- YV5151 is a simple, quick and accurate test for the assessment of EONS that permits earlier treatment of those newborns at higher risk, but also avoids unnecessary treatment of newborns at no risk.
- This diagnostic test can be easily incorporated into routine newborn testing, as cord blood sampling is used to monitor cord blood gases at delivery.
- US Application filed

YV4925: Early Detection of β Cell Death

PARTNERED

Principal Investigator: Kevan Herold, MD

Background:

- Monitoring β cell death is critical for managing diabetes, which affects millions globally.
- Current diagnostic methods lack specificity for detecting ongoing β cell death.
- New biomarkers and diagnostic methods for differentially methylated circulating DNA overcome these limitations.

Indications: Diabetes, β cell death monitoring

Innovation & Asset:

- **Specific Biomarkers:** Identifies ongoing β cell death in diabetic patients.
- **Diagnostic Precision:** Enhances monitoring accuracy for diabetes management.
- **Proven Efficacy:** Validated through comprehensive research studies.
- **Broad Application:** Useful for various types of diabetes.

IP: Multiple national patents issued: US 10,125,394; EP 2723901; HK 1195590B

Reference: Proc Natl Acad Sci USA. 2011 Nov 22;108(47):19018-23

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Devices, Methods, Models & Assays

YV8886: Endobronchial Blocker with Multiple Features to Assist with Treatment of Hemoptysis

Principal Investigator: Peter Kahn, MD, MPH (peter.kahn@yale.edu)

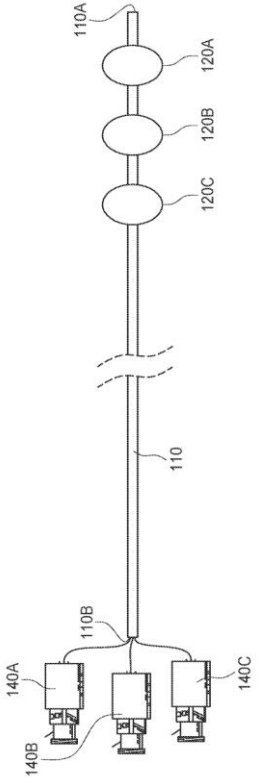
Background:

- Lung isolation for ventilation control is critical in thoracic surgery and critically ill patients suffering from lung diseases like pneumonia, which affects millions worldwide.
- Current methods involving an endotracheal tube, a balloon-tipped single or double-lumen catheter, have limitations including challenging placement, risk of traumas, and high-pressure damage to lung tissues.
- This new technology offers an endobronchial blocker featuring multiple balloons and improved lumens that ensure efficient, safe, and flexible lung isolation.

Indications: Thoracic surgery, lung infections (pneumonia), lung bleeding (hemoptysis), pneumothorax (collapsed lung)

Innovation & Asset:

- **Enhanced Isolation:** Three-balloon design increases reliability and reduces complications.
- **Easily Positioned:** Compatible with standard single lumen endotracheal tubes, simplifying patient setup.
- **Improved Safety:** Low pressure balloon reduces risk of bronchial trauma and better maintains positioning.
- **Repositionable:** Easily repositioned if dislodged, reducing the need for reinsertion and associated risks.
- **Enhanced Control:** Flexible distal portion allows precise placement with a fiberoptic bronchoscope.
- **Versatile Application:** Can be used for both right and left mainstem bronchus isolations, adapting to various clinical scenarios.
- **Patent Filings:** US Patent Pending App # 18/616,372



YV8864: Delivery of Nebulized Medications Sequentially or Simultaneously

Principal Investigator: Peter Kahn, MD, MPH (peter.kahn@yale.edu)

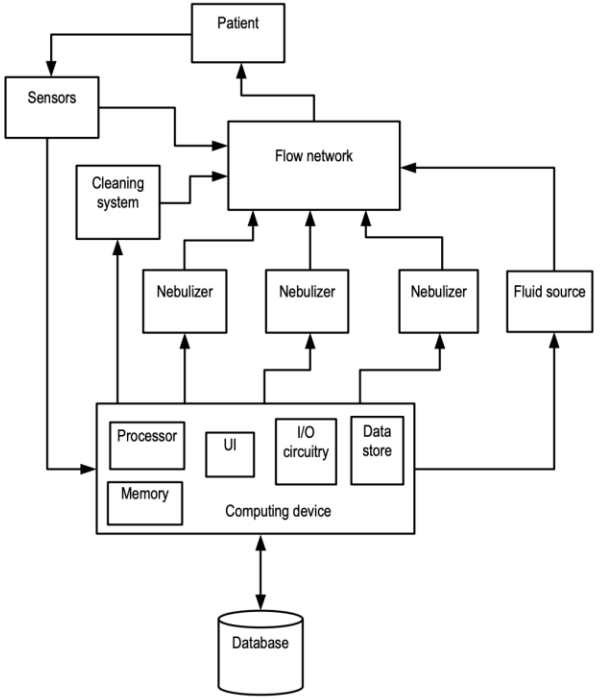
Background:

- Respiratory diseases such as asthma and COPD affect approximately 10% of the global population. These diseases require effective medication delivery systems to target lung tissues directly.
- Current standard of care involves inhalers and non-digital nebulizers, which can be inefficient and imprecise, leading to suboptimal dosing and increased risk of side effects.
- This new technology offers an advanced system for the precise and efficient delivery of nebulized medications, improving patient outcomes by ensuring accurate dosing and reduced exposure to surrounding personnel.
- In many diseases, patients require the nebulization of multiple medications. This technology allows for automated delivery of multiple medications in sequence, enhancing treatment efficiency.

Indications: Asthma, COPD, pulmonary fibrosis, cystic fibrosis, bronchiectasis

Innovation & Asset:

- **Muli-Nebulizer Technology:** multiple nebulizers facilitate concurrent or sequential medication delivery.
- **Integrated Sensors:** Monitors patient's exhalation and flow rates for adaptive treatment.
- **Automated Cleaning System:** Ensures hygiene and reduces maintenance.
- **Portable Design:** Enhances patient mobility and compliance.
- **Smart Connectivity:** Allows remote monitoring and adjustment of treatment plans by healthcare providers.
- **Patent Filings:** US Patent Pending App # 18/581,816



YV8818: Providing Individualized Delivery of Suspended Aerosol Medication

Principal Investigator: Peter Kahn, MD, MPH (peter.kahn@yale.edu)

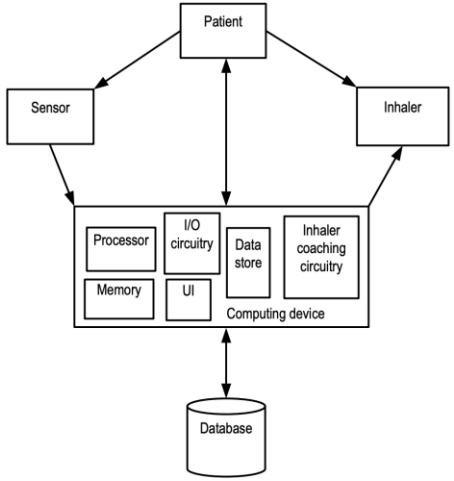
Background:

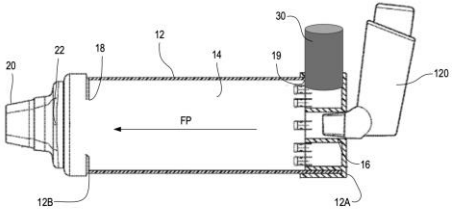
- Asthma and COPD affect over 330 million people globally, and the most common treatment is the use of an inhaler, which delivers medication directly to the lungs. However, improper inhaler use remains a major contributor to poor disease management and outcomes.
- Traditional inhalers often lead to user mistakes like incorrect timing and poor breath coordination, reducing medication efficacy.
- Current valved holding chambers do not allow for individualized flow generation, thus limiting the users of this technology to those who can generate higher peak flows.
- This new technology provides individualized delivery of suspended aerosol medication, synchronizing with the patient's respiratory cycle to ensure effective drug delivery.

Indications: COPD, Asthma, Respiratory Inflammation

Innovation & Asset:

- **Individualized Delivery:** Precisely matches medication delivery with patient's breathing patterns.
- **Smart Integration:** Integrates with any type of inhaler, addressing multiple respiratory diseases with a single solution.
- **Data Sharing:** Facilitates patient data sharing with healthcare providers, supporting evidence-based treatment adjustments.
- **Outcome Monitoring:** Tracks clinical outcomes like symptom relief and lung function improvement, enhancing patient care.
- **Environmental Initiatives:** Evaluates and recommends environmentally friendly inhalers, reducing the carbon footprint.
- **Patent Filings:** US Patent Allowed App # 18/389,897





YV8739: Systems and Methods For Coaching Inhaler Use Via Synchronizing Patient and Respiratory Cycle Behaviors

Background:

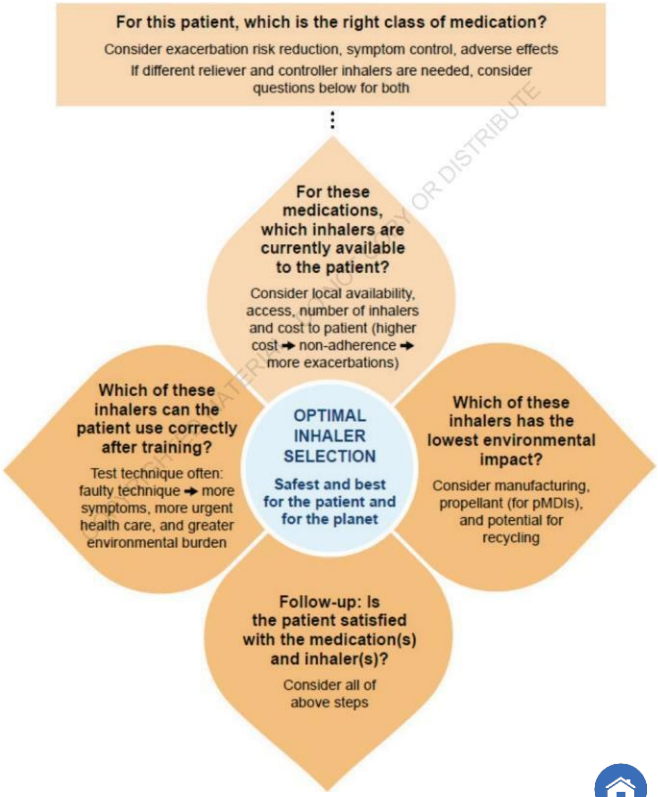
- Proper inhaler technique is essential for effective management of respiratory conditions.
- Incorrect inhaler use is a widespread issue that can worsen disease control and lead to increased exacerbations.
- There are no comprehensive digital tools available that provide assistance with inhaler selection, usage, and ensuring effective inhaler use.

Innovation & Asset:

- An advanced system is designed to improve inhaler use for medication delivery.
- Utilizes sensors to collect and analyze patients' respiratory behavior to determine the best timing for inhaler use.
- The system evaluates and refines the effectiveness of each inhalation, tailoring it to the individual's breathing patterns and historical data.
- It takes into account the environmental impacts of inhaler use and suggests eco-friendlier options when possible.
- Incorporates various sensory signals and has the capability to automate the actuation of the inhaler for a personalized and efficient medication delivery experience.

Patent Filings: Patent Claims Allowed, Issue Date Pending

Inventor: Peter Kahn MD MPH, (peter.kahn@yale.edu)



Robert Migliorini, J.D. / robert.migliorini@yale.edu
Image Source: https://ginasthma.org/2023-gina-main-report/
Yale

YV8630: Machine Learning System and Method For Attendance Risk Mitigation

Background:

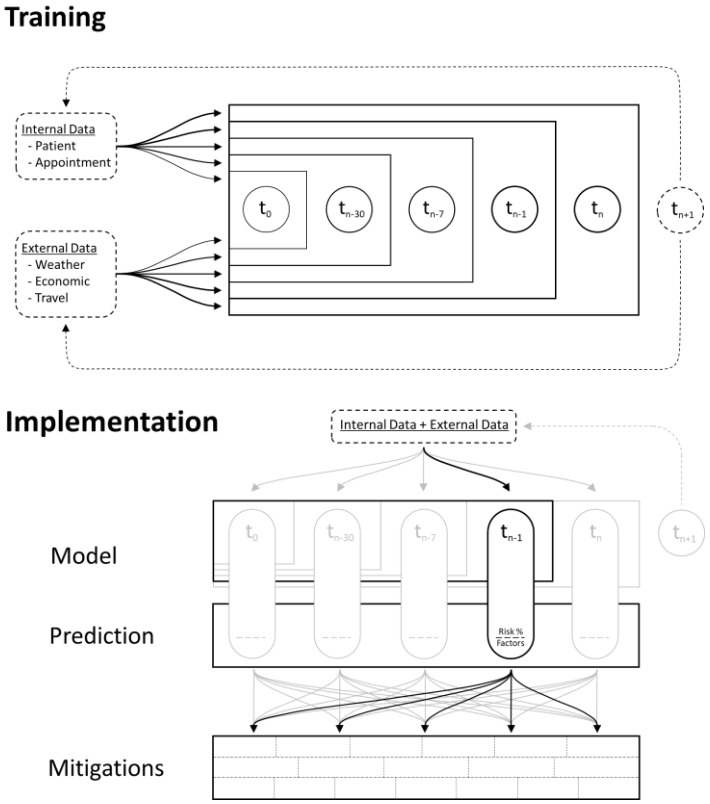
- Patient no-shows to clinical or related appointments are profoundly detrimental to health outcomes, provider morale, clinic efficiency, and financial outcome measures.
- Appointment attendance is influenced by a broad number of factors, both intrinsic (patient, appointment) and extrinsic (clinic, weather, economics travel) to the patient.
- Prediction and mitigation strategies for no-shows are challenging to operationalize and therefore have not been deployed to date.

Innovation & Asset:

- Machine learning model trained on electronic medical record data as well as blended stream of relevant external data to predict no-show at multiple time points.
- Model suggests intervention strategies to decrease likelihood of no-show tailored to factors contributing most to high no-show risk, for that individual, at given timeframe, and responsive to patient preference.
- Mitigation strategies are deployed recursively and adapted in real-time along with recalculation of no-show prediction probability to best mitigate risk of no-show.

Patent Filings: Patent Claims Allowed, Issue Date Pending

Inventors: Peter Kahn, MD MPH (peter.kahn@yale.edu)
Walter Mathis, MD (walter.mathis@yale.edu)



YALE VENTURES

Robert Migliorini, JD (robert.migliorini@yale.edu)

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YV8519: Novel methodsof human microbiota genotoxin analysis

Principal Investigator: Noah Palm, PhD

Background:

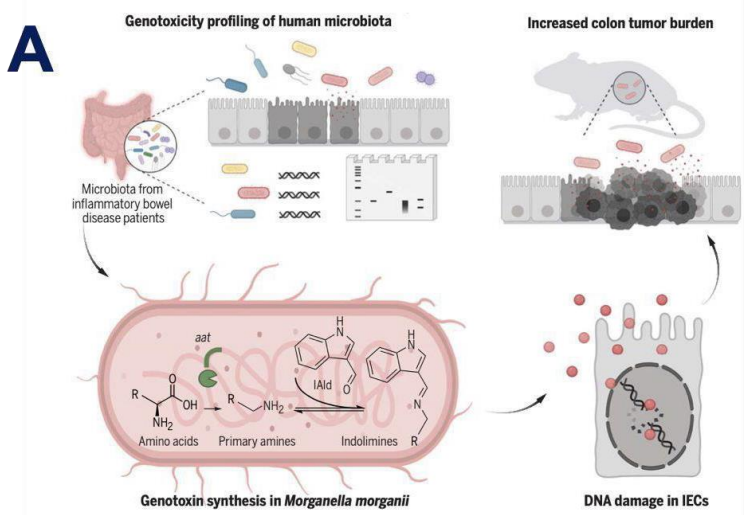
- Small molecule metabolites of the gut microbiome may increase colorectal cancer (CRC) risk
- Current approaches of metagenomics and 16s rRNA sequencing do not provide directly causal information about DNA damage

Indications: CRC (novel genotoxin family identified) & novel therapeutic target discovery

Innovation & Asset:

- **New target family:** Identifies novel CRC genotoxins.
- **Systemic approach:** Provides causal, mechanistic data on DNA damage.
- **Proven efficacy:** Discovered indolimines in *M. morganii* (**A**).
- **Scalable method:** Large-scale identification of genotoxic microbes.
- *Full Publication in Science*

IP: PCT/US2023/76213



Using a novel combination of electrophoresis-based methods to analyze DNA-damaging properties of microbes, a new family of genotoxins was identified in the bacteria *Morganella morganii*. This species contributes to colorectal cancer development in patients with Inflammatory Bowel Disease. The discovery heralds both a novel colorectal cancer target and a powerful method for identifying future genotoxic targets in other conditions.

YV8510: Novel Wet Adhesives Derived from Bacterial Biofilm

Principal Investigator: Jing Yan, PhD & Rich Olson, PhD

Background:

- Adhesive materials are essential in wet environments, yet current options are often ineffective and sensitive to oxygen and pH levels.
- Biofilm derivatives offer a novel solution, demonstrating strong adhesion in diverse conditions.

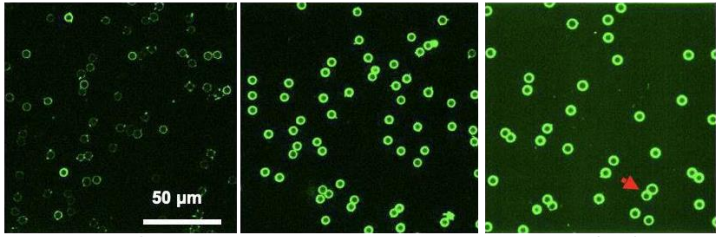
Indications: Underwater engineering (ship materials, underwater vehicles, etc.) & biological applications (catheters, stents, bone repair, grafts, heart valves, etc.)

Innovation & Asset:

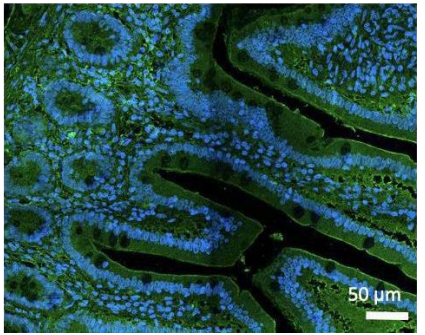
- **Bio-adhesives:** Derived from Vibrio biofilm.
- **Versatile use:** Suitable for abiotic **(A)** and biotic **(B)** applications.
- **Integrated proteins:** Can be combined with recombinant proteins.
- **Mass production:** Easily produced through chemical synthesis or bacterial expression.
- **Environmental stability:** Performs well in various conditions.

IP: PCT/US2023/074691

A The biofilm-derived peptide can spontaneously adsorb onto various abiotic surfaces, and glue various microspheres together.



B The biofilm-derived peptide can adhere to human tissue surfaces, among other biotic surface tested. The peptide shows no toxicity towards animal organoid culture.



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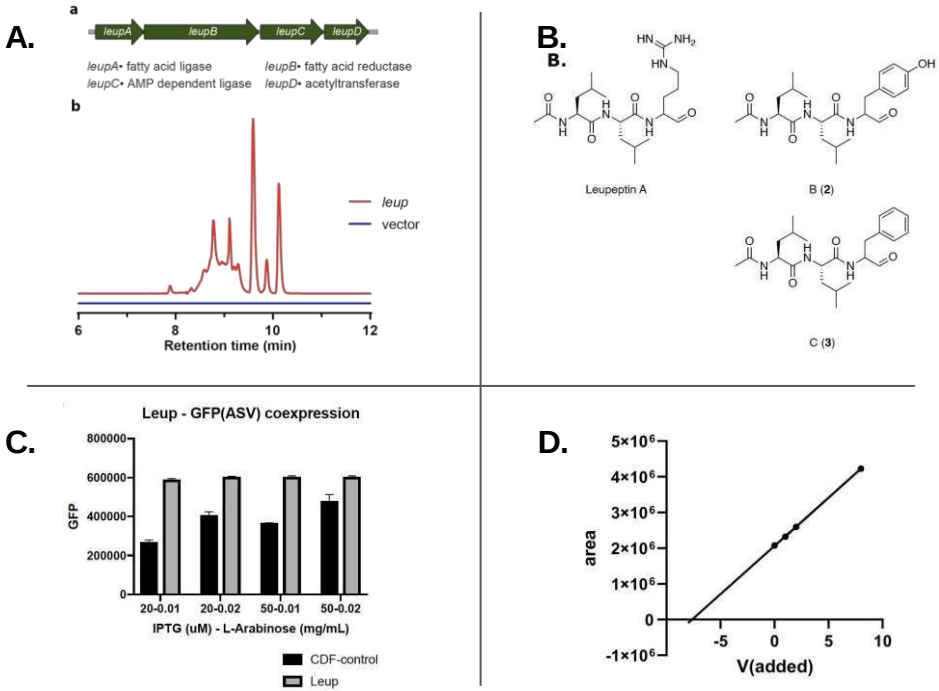
YV7917: System for Enhanced Production of Leupeptins in E. coli

- **Principal Investigator:** Jason Crawford & Lab Interests
- **Leupeptins can now be abundantly produced in *E. coli***
  - Single plasmid (A) system for the stable abundant (D) expression of leupeptins in in E. coli.
  - Leupeptin A production level is in excess of 70 mg/L in LB.
- **Co-expression of leupeptin pathway is able to produce more intact protein in E. coli (C)**
  - Co-expression leup and degradation-sensitive GFP variant provided higher GFP production at 20 deg C.
- **Leupeptin A production level is high in E. coli fermentation (D)**
- **Intellectual Property**
  - Compositions, methods of manufacture and uses.
  - Heterologous production in E. coli
  - Engineering the pathway for leupeptin B, C production

IP: issued US patent: 11,912,742



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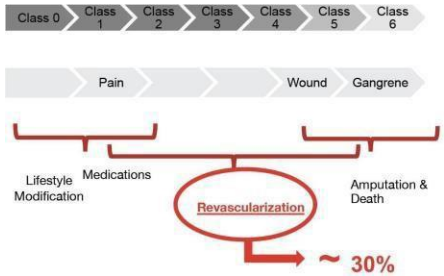
YV7894: Multidirectional Sheath for PAD

Principal Investigator: Alan Dardik M.D., Ph.D

Peripheral Arterial Disease (PAD) is a major Public Health Crisis:

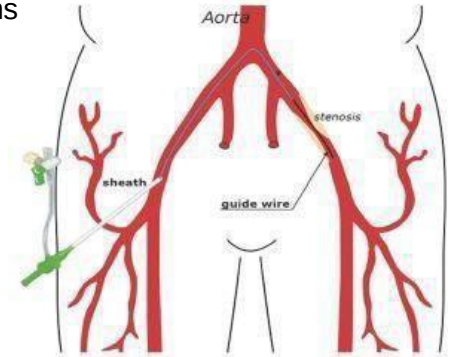
- PAD Patients > 200 million worldwide Majority are over age 65 (double by 2040)
- ~900,000 PAD procedures per year
- ~ 57% are reinterventions



Current Practice for all PADprocedures (diagnostic and interventional) is **unidirectional ONLY** (Medtronic, Cordis, Terumo, Cook, Merit).

DeTour Sheath allows **bi-directional** diagnosis and intervention in the same procedure:

- Overall **cost savings** for hospitals and outpatient centers (~$250 million per year)
- ↓ Totalnumber of interventions & use of closure devices
- ↓ Access site complications by **50%**
- Projected Sheath Cost per unit (~ $150)



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YALE VENTURES

YV7209: Inducible gene expression system for commensal bacteria

Principal Investigator: Andrew Goodman, Ph.D.

Background:

- Gene expression systems for gut bacteria, particularly Bacteroides, are crucial for understanding and manipulating gut microbiota.
- Existing systems lack precision and versatility, limiting therapeutic and research applications.
- New system induces gene expression 5 orders of magnitude above background, working effectively in various Bacteroides species and different microbial environments.

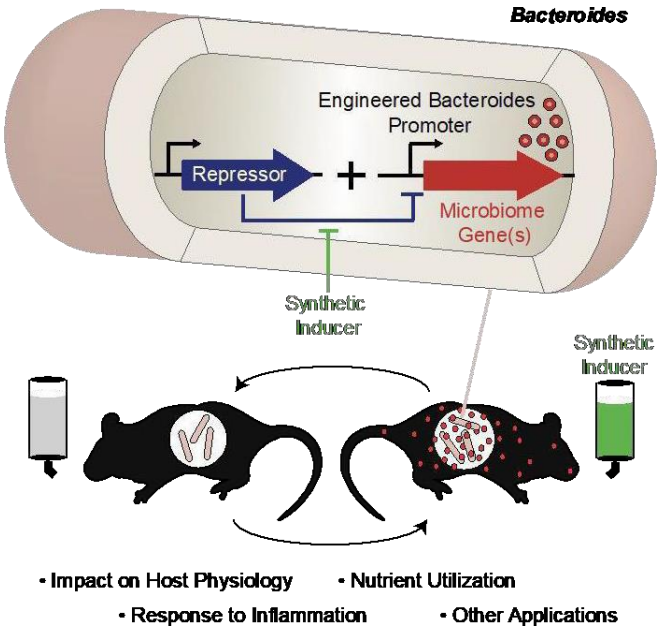
Indications: Gut microbiota research, therapeutic delivery via commensal bacteria

Innovation & Asset:

- **High Induction:** Gene expression increased 5 orders of magnitude above background.
- **Broad Efficacy:** Effective in 11 Bacteroides species.
- **Versatile Use:** Works in monocolonized and fully colonized mice models.
- **Therapeutic Potential:** Can deliver therapeutic agents through commensal bacteria.

IP: US Patent: 11,549,115

Reference: Lim, Bentley et al. Engineered Regulatory Systems Modulate Gene Expression of Human Commensals in the Gut. Cell, 169, 547 - 558. e15(2017)



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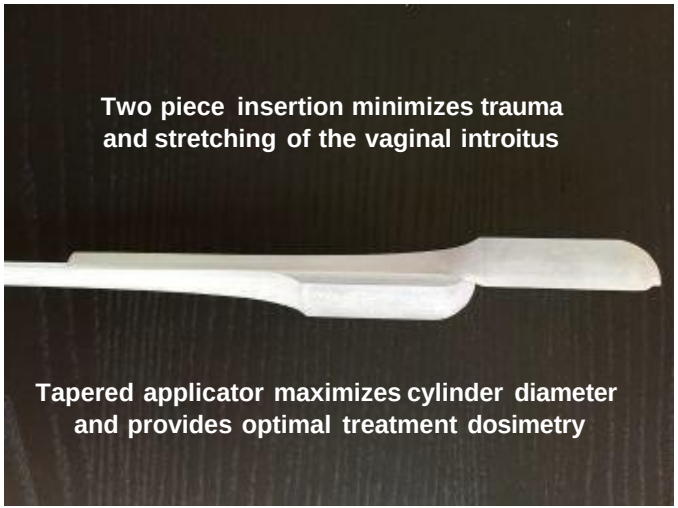
YV7116: Yale Tapered Applicator for Improved Intravaginal Brachytherapy

Principal Investigator: James Yu, M.D.; Amandeep Mahal

A Novel Brachytherapy Applicator for Improved Quality of the Treatment of Endometrial Cancer

- Thereare an estimated 61,380 new casesof endometrial cancer every year, typically in post-menopausal women.
- Standard treatmentof endometrial cancerafter surgery requires the direct application of radiation internally (known as “intravaginal brachytherapy”).
- Ideal radiation treatment occurswhenthe largest diameterof cylinder is used
- Current applicators of radiation therapy are cylindrical, uncomfortable, and limitedat times bypatient anatomy
- Patient comfortimpacts treatment adherence, caregiver impression, and overall sense of well being.



IP status: US Patent Application. 62/478,341

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YALE VENTURES

YV7111: PremieBreathe

Principal Investigator: Anjelica Gonzalez, Ph.D.

Portable Compact High Flow Nasal Cannula (HHFNC) Therapy for Neonates and Infants

- Affordable, breathing aid to support newborns suffering from respiratory distress in resource-limited facilities.
- PremieBreathe avoids complications that result fromconventional bCPAP nasal cannula and dry cold high pressure, such as nasal trauma including granulation, ulceration of the nostrils, and distended abdomen which can lead to malnutrition.
- UV water sterilization mechanism eliminates bacterial contamination.
- Mobile unit replicates the outputs of commercial immobile devices for approximately 1/10 of the cost, or $500

premiebreathe

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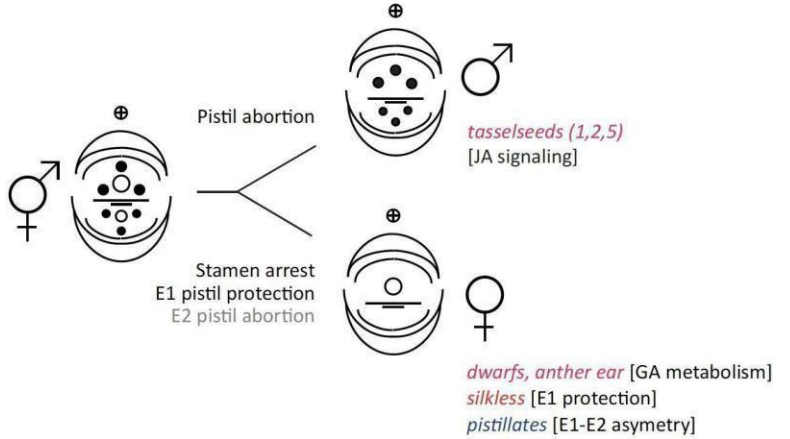
YV7073: Control of sexuality by Sk1 gene

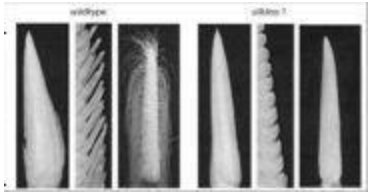
Genotype independent hybrid cereals

The Silkless gene *Sk1* is a maize sex determination gene, the first single gain-of-function gene known to control survival of functional pistils. It enables production of unisexual flowers (either staminate or pistillate on separate plants) in cereal crops.

- Lower cost of development for hybrid seed through outcrossing of unisexual plants. Only one generation of gene-editing per inbred, instead of 6-8.
- More efficient production of hybrid seed through wind pollination of unisexual flowers.
- Profound implications for food security increasing crop yields by 20-40% without placing additional land under production.
- Better abiotic stress resistance and disease resistance.
- Limited only by resources vs. current hybrid sterility systems which are genotype and environment-dependent.



Control of Sexuality by Sk1- encoded UDP glycosyltransferase. System includes a second herbicide resistance marker gene that enables identification of the transgenic cells in tissue culture and selection of transgenic plants for new breeding lines (visual pigmentation of seed/seedling).



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YALE VENTURES

YV6556: Heart Failure Recovery (HFR) Device

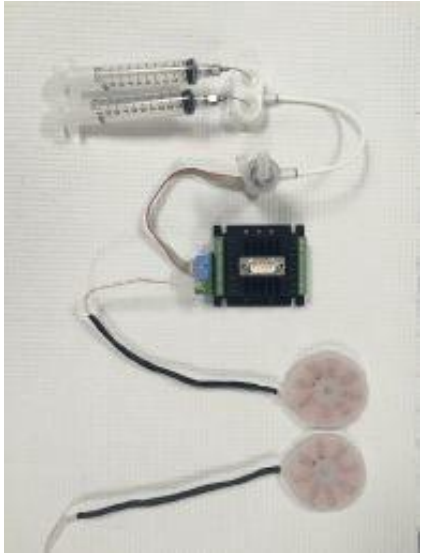
PARTNERED

Principal Investigator: Pramod Bonde, MD

Heart Failure Recovery (HFR) Device

A device specifically designed to prevent readmissions and in hospital stay of patients with congestive heart failure

- Insertion under local anesthesia: key hole approach (minimally invasive)
- On demand device to treat CHF exacerbation.
- Subsequent office based care (no need for admission to hospital)
- Robust circulatory support to help tailor medical therapy.
- Avoids adverse events (pump thrombosis, GI bleeding, strokes and infection) that plague current LVAD devices (HeartMate, HertWare, Jarvik and MicroMed Debakey pumps)
- Device battery charged/powered wirelessly with no need for any dressing changes/external leads.
- */nternational PCT patent application 'Heart Failure Recovery Device and Method of Treatment'*



The HFR device include a pump, a coil for wireless charging and a purging system to start/stop & clean the pump without surgery.

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YV6517: Human Matrix-Polymer Scaffold

Principal Investigator: Anjelica Gonzalez, PhD

PEGylated Amnion scaffold for use in wound management

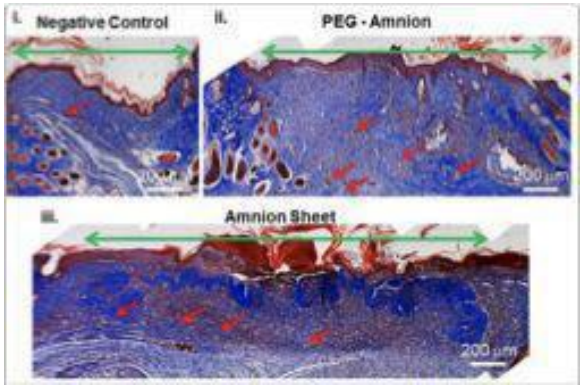
A wound repair hydrogel that combines the benefits of amnion 'scarless healing' with a hydrogel scaffold that conforms to the wound.

Advantages compared with amnion sheet:

- Significantly less wound contraction.
- 2 x fastersurfaceclosure.
- Lower infection risk(animal data).
- 8 times less amnionused.
- Utilizes FDAapproved materials.
- Conforms to thewound and provides greater shear strength in healing.

→ **Can be applied as a gel and cured in white light**

→ **or as a prefab dressing providing a much longer shelf-life than amnion sheets.**



The scaffold (II) shows better performance than decellularized skin and skin grafts on animal models.

Applications: diabetic foot ulcers; corneal repair; burn wounds.
The mechanical properties of the hydrogel (mechanical stiffness of the scaffold, individual pore size and porosity) can be tuned through a crystal templating method developed at Yale.

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YALE VENTURES

YV6462: Novel Endovascular Retrieval Device for Inferior Vena Cava Filter

Principal Investigator: Cassius Iyad Ochoa Chaar, MD

Background:

- *Inferior Vena Cava (IVC) filters* save lives by preventing pulmonary embolism in ~250,000 patients annually in the U.S.
- Standard care retrieval techniques using a snare often fail due to filter tilt, penetration, or scarring, leading to a 20% failure rate.
- The *novel Endovascular Retrieval System* resolves IVC filter retrieval issues, improving success rates and patient safety.

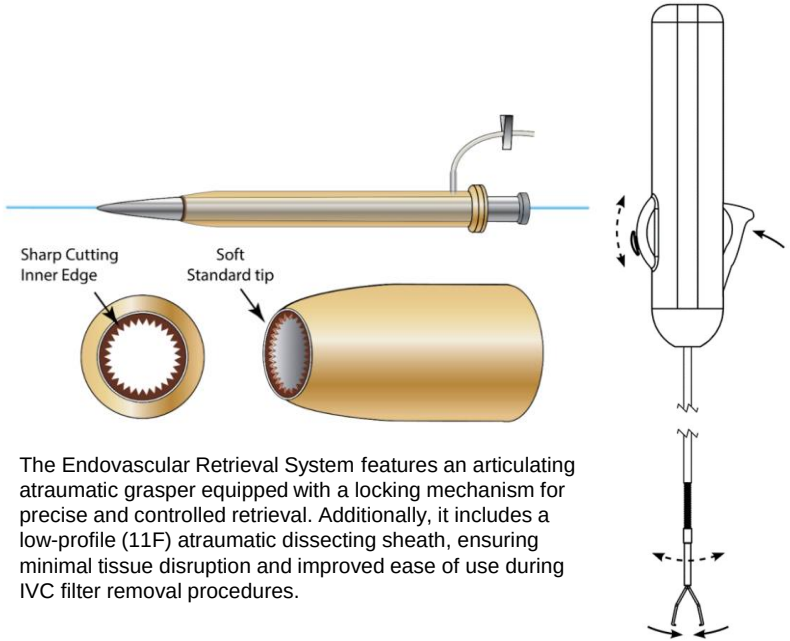
Indications: Pulmonary embolism prevention, IVC filter retrieval failure, tilted/permanent IVC filters

Innovation & Asset:

- **Articulating Grasper**: Atraumatic grasper with a locking mechanism for precise control.
- **Low-Profile Design**: 11F atraumatic dissecting sheath enhances ease of use.
- **Superior Retrieval**: Proven efficacy in *tilted* and *permanent IVC filters* where standard devices fail.
- **In Vivo Validation**: Porcine model results demonstrate superior retrieval performance.
- **Large Market Potential**: $100M U.S. market with 250,000 IVC filters placed annually.

IP: US Patent: 10,524,891

Learn More: Yale Life Sciences PitchFest



The Endovascular Retrieval System features an articulating atraumatic grasper equipped with a locking mechanism for precise and controlled retrieval. Additionally, it includes a low-profile (11F) atraumatic dissecting sheath, ensuring minimal tissue disruption and improved ease of use during IVC filter removal procedures.

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YALE VENTURES

YV6109: Catalyst-Dependent Synthesis of Glycopeptide Derivatives

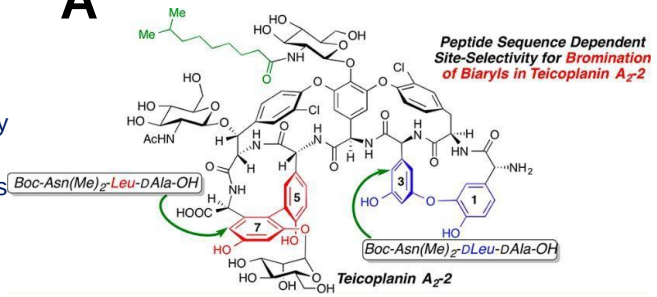
Principal Investigator:

Scott Miller, PhD

Background:

- Glycopeptide analogues may overcome Vancomycin resistance in Staphylococcus & Enterococcus but are difficult to selectively synthesize

A



B

Entry	Compound	MSSA[a,b]	MRSA[c]	VSE[d]	VRE (VanB)[e]	VRE (VanA)[f]
1	Vancomycin	0.5	1	2	16	>64
2	Teicoplanin	0.5	0.5	0.25	0.25	>64
3	Teicoplanin A_2-2	0.5	0.5	0.25	0.25	>64
4	7	0.5	1	0.5	1	>64
5	9	0.5	1	0.25	0.5	>64
6	10	1	1	0.5	1	>64
7	14	2	2	4	8	>64
8	16	0.25	0.25	0.25	0.5	>64
9	20	0.25	0.25	0.12	0.12	32
10	17	0.25	0.25	0.12	0.25	>32
11	18	0.5	0.5	0.25	0.5	>64
12	19	4	2	1	0.5	32
13	21	8	4	0.5	0.25	8
14	22	8	4	0.5	0.25	1
15	Linezolid	4	4	2	2	2

[a]MIC values reported in μg/mL. [b]MSSA = methicillin-susceptible *S. aureus*, ATCC 29213. [c]MRSA = methicillin-resistant *S. aureus*, ATCC 43300. [d]VSE = vancomycin-susceptible enterococci, ATCC 29212. [e]VRE = vancomycin-resistant enterococci, ATCC 51299. [f]MMX 486.

Indications: Novel antibiotic development & compounds

Innovation & Asset: Method of halogenating and cross-coupling glycopeptide antibiotics:

- Demonstrated efficacy using small peptide promoters to selectively brominate the glycopeptide teicoplanin (A)
- Two-step process with yields between 28 - 43%
- Promising minimum inhibitory concentration data from generated compounds (B)

IP: issued US patent: 10,294,275

Novel compounds developed from teicoplanin via selective halogenation with or without cross-linking demonstrate potent activity against five strains of gram-positive cocci. Notably, compounds 21 & 22 (entries 13 and 14) inhibit VanA VRE, which is both vancomycin and teicoplanin resistant.

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YALE VENTURES

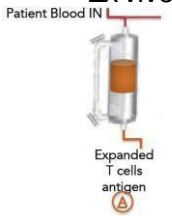
YV4699: T-cell expansion system

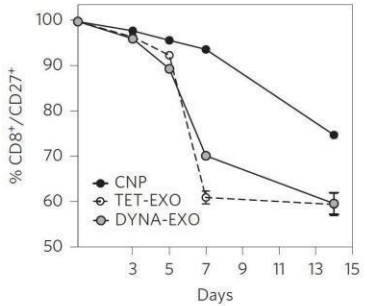
Principal Investigator: Tarek Fahmy, Ph.D.

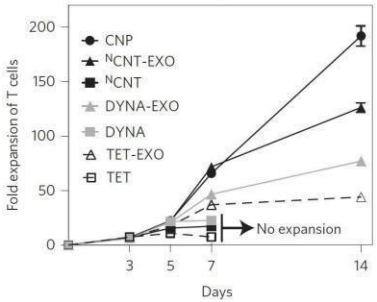
Biomimetic Lymph node

Advances a Non-Engineered approach to adoptive cell therapy (tailored multi-targeting of antigen-specific immune/regulatory signals).

- All-in-one expansion and activation reduces contamination risk, eliminates operator and open handling of material.
- Single-use disposable cartridges permits bedside incubation.
- Current Car-T products in clinical trials require separate offsite cell manipulation steps (eg. Dynabeads™, GE Wave ™).
- Paracrine delivery of IL-2 lowers T cell exhaustion.
- Ex-vivo 'lymph node' structure consists of a heterogeneous nanoparticle substrate (CNP):
  - T-cells are expanded **10x faster** and are **3x more potent** than current methods for T-cell expansion
  - The percentage of T-cells **activated** by CNP is above 90% in the first week – *top figure*
  - Continuously better at T-cell expansion than other methods in vivo – *bottom figure*
  - Uses 1 ng of reagents for 1 million cells
  - Uses 1000x less of T-cell growth factor IL-2







US Patents 9,737,593; 8,629,098 'Compositions and methods for adoptive and active immunotherapy'

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Thank You