Yale University Innovation Pipeline

Biomedical

YALE VENTURES

Table of Contents

Oncology

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])

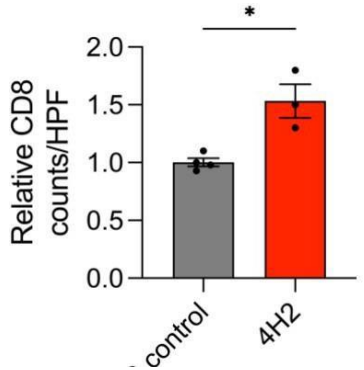
Innovation & Asset: Cytoplasmic anti-Guanine antibody, 4H2:

- 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: Patent Pending

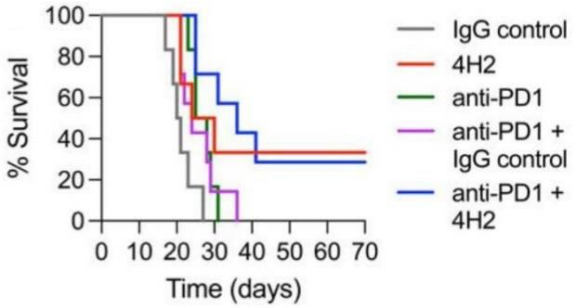
A

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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YV8604: Novel Methods of CAR-T Improvement

Principal Investigator: Xiaolei Su, PhD

Background: Chimeric Antigen Receptor T (CAR-T) cell Therapy

- Low antigen sensitivity of CAR-Tcells limits their use to high-antigen cancers and causes increased rates of cancer relapse.

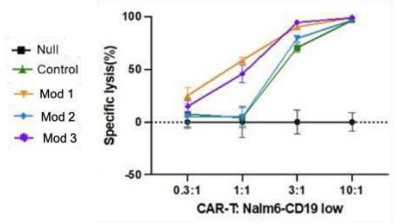
Indications: CAR-Ttherapy improvement

Innovation & Asset: Sensitization of CAR-Tcells via fusion of a novel group of motifs to existing CARs

- Broad application that can be used with any CAR
- Increased in-vitro cytotoxicity demonstrated in multiple cancer lines: CD19 CAR-T in Nalm6 cells with low CD19 expression (**A**) & HER2 CAR-T in HT29 cells (**B**), NCI292 cells, K562 cells
- Increased in-vivo tumor inhibition using CD22 CAR-T in Nalm6-xenografted mice (**C**)
- No change in T-cell exhaustion markers vs unmodified CAR-T cells (dns)

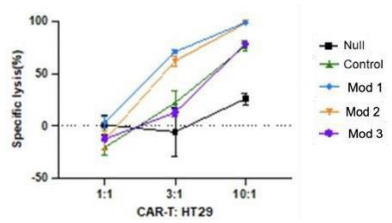
IP: Patent application pending

A



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

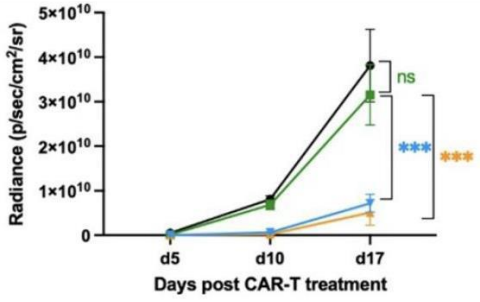
B



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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YV8466: Targeting Virally-Driven Cancer with an mRNA Vaccine

Principal Investigator: Jeffrey Ishizuka, MD, DPhil

Background: Aggressive, frequently lethal malignancy (undisclosed)

- A high proportion of cases are attributable to viral infection

Indications: Virally-mediated malignancy

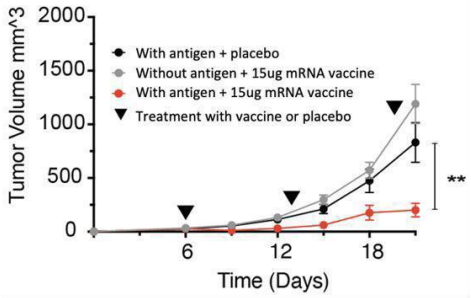
Innovation & Asset: Novel mRNA vaccine targeting an oncogenic, virally-encoded antigen

- Vaccine administration causes antigen-specific tumor burden reduction (**A**) and increased survival (**B**) in mouse models
- In human cancer patient co-cultures, dendritic cells transfected with the mRNA vaccine cause beneficial T-cell changes
  - Induce CD8+ T cell expansion & memory phenotype
  - Stimulate T-cell IFN-γ release & tumor cell killing (**C**)
- mRNA approach offers improved immunogenicity, flexibility, and economical synthesis

IP: Patent application pending

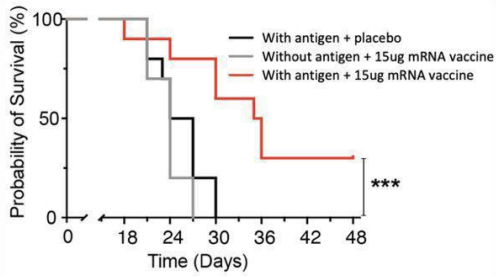
A

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



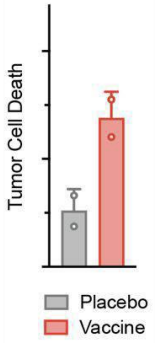
B

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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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)

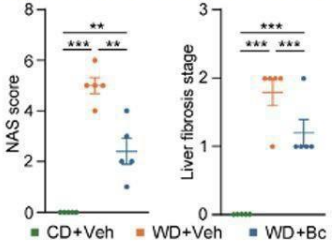
Indications: NASH, fibrosis, anorexia, depression, endometriosis

Innovation & Asset: Small-molecule Bobcat339 (Bc) degrades TET3 protein

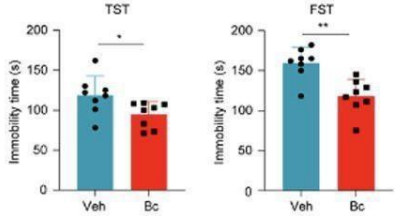
- Decreases NASH/fibrosis (A) and depressive behaviors (B)
- Improves appetite (C) and body weight (D) in an activity-based mouse anorexia model
- No toxicity, well-tolerated

IP: Patent application pending

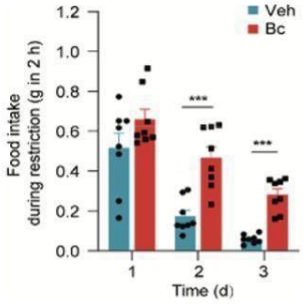
A Mice treated with Bc had decreased NFLD activity score (NAS) and fibrosis stage. WD, a western diet used to induce NASH.



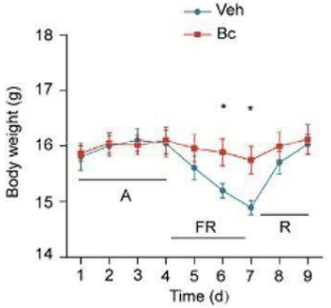
B Mice treated with Bc had improved performance on tail suspension test (TST) and forced swim test (FST), which evaluate the impact of depression on behavior



C Mice treated with Bc had increased food intake during the food-restriction (FR) period



D Mice treated with Bc maintained normal weight during the FR period



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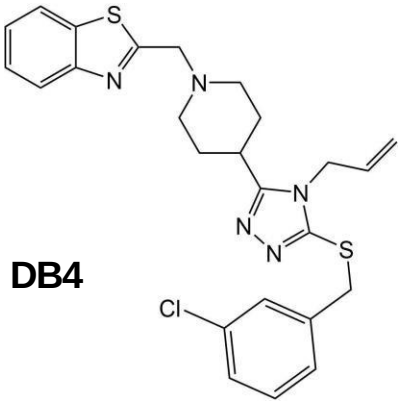
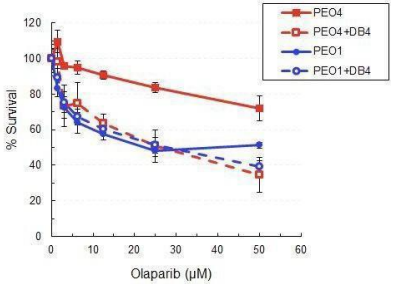
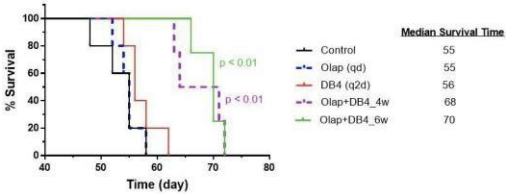
YV7950: Novel Small Molecule Inhibitor for Treatment of PARP inhibitor-Resistant Ovarian Cancer DB4

Principal Investigator: Elena Ratner

- PARP inhibitors (PARPi) are FDA-approved targeted drugs for ovarian and breast cancers with BRCA
- mutations or homologous recombination (HR) repair deficiency.
- However, at least 50% of ovarian cancer has no HR deficiency and is resistant to PARPi therapy. Furthermore, PARPi-sensitive cancers can potentially restore HR repair and develop resistance to PARPi in patients.
- Dr. Elena Ratner's lab at Yale performed in silico screening and discovered a novel small molecule inhibitor DB4 that blocks HR repair and renders PARPi-resistant cancer cells hypersensitive to PARPi, such as olaparib and niraparib.
- Combination of DB4 and olaparib efficaciously suppresses the progression of PARPi-resistant ovarian cancer xenografts and significantly prolongs the survival time of mice.
- **Intellectual Property:** Patent application pending
- **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 drug alone had no effects compared with vehicle-treated control mice.

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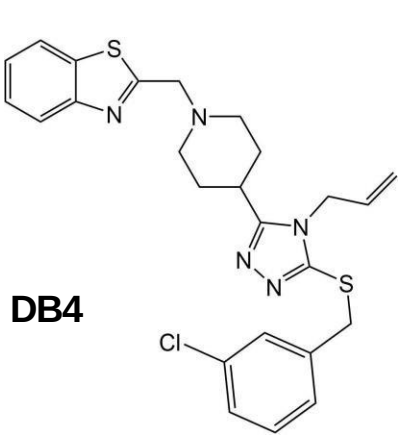

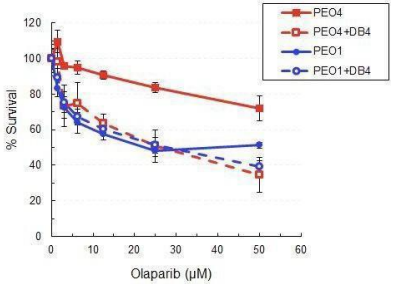

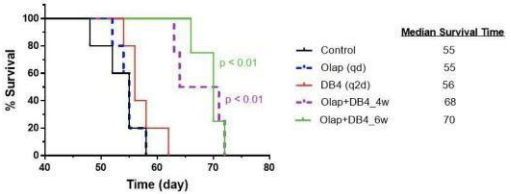

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YV8438: Novel Target for the Treatment of Renal Cell Carcinoma

Principal Investigator: Rachel Perry, PhD

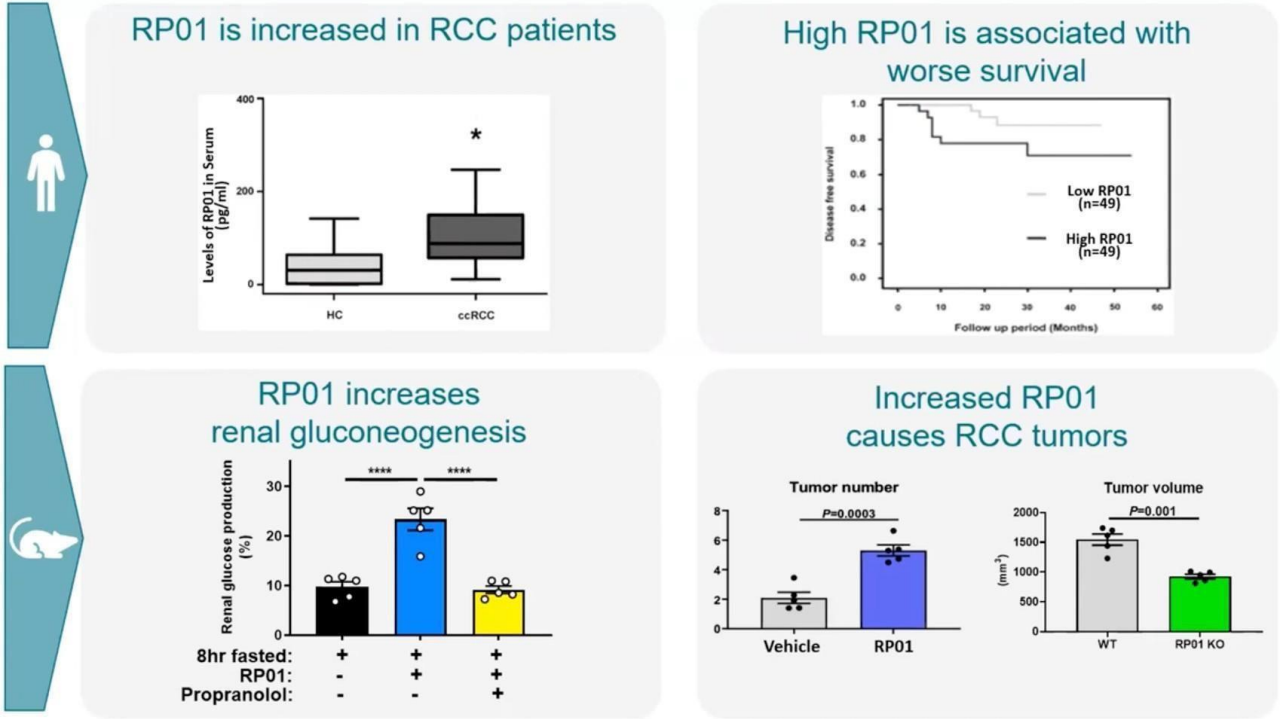
Background:

- Renal Cell Carcinoma (RCC) often presents in Stage IV, which has poor survival and limited treatment options

Indications: Renal Cell Carcinoma

Innovation & Asset: Novel metabolic target, RP01, is implicated in RCC pathogenesis

- RP01 is increased in RCC patients and associated with worse survival
- RP01 increases renal gluconeogenesis via beta-adrenergic signaling (inhibition of gluconeogenesis can be used as a go/no-go strategy)
- RP01 infusion increases RCC tumor count in genetically-predisposed mice, while RP01 KO mice have reduced tumor burden
- RP01 is a prime candidate for monoclonal antibodytargeting



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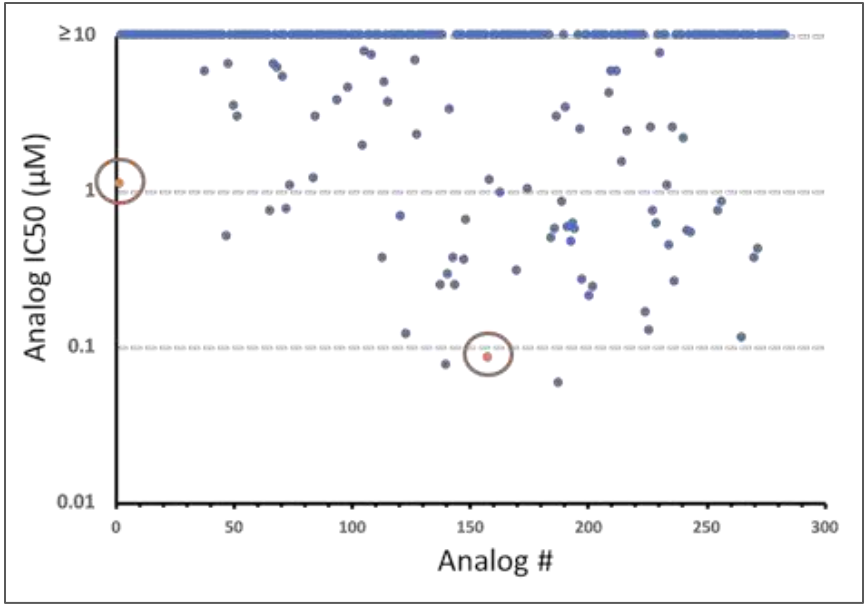
YV7888: First in Class Glycosylation Inhibitors for the Treatmentof Cancer

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.



Patents: US1 0765638B 2; WO2017019540A2

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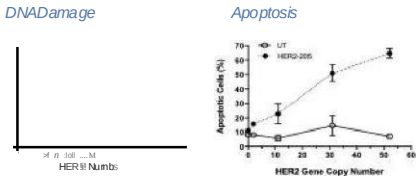
YV6196; 7509: Targeted Therapeutics for Cancers With Gene Amplification

Principal Investigator: Faye Rogers, Ph.D.

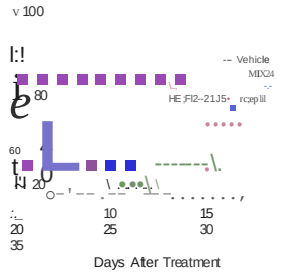
Gene amplification is a critical factor driving major oncogenic processes. Major drug breakthroughs in oncology such as Herceptin, Gifetinib, target the proteins encoded by amplified genes. **The problems** with the current approach: 1. Protein overexpression is a requisite for drug activity; 2. Many proteins are undruggable by small molecule drugs; 3. Prone to the primary and/or acquired drug resistance.
Our approach is to directly target the amplified DNA and manipulate the DNA damage response to **trigger apoptosis In cancer cells.** We developed damage-inducing oligonucleotides (DIOs) that directly convert amplified oncogenes to excessive DNA damage and activate apoptosis in cancer cells. DIOs **target** specific polypurine sites in the amplified cancer genes. **Mechanism of Actilon:** sequence-specific gene targeting and DNA damage to induce p53-independent apoptosis in cancer cells.
DID advantages: 1. Hijacking cell's own machinery, 2. Reduces normal tissue toxicity and off-target effects, 3. Independent of protein cellular function; 4. Multiple cancer types can be targeted with our DIO approach: 461 amplified genes; 14 cancer subtypes; 519, 971 unique DIO targeting sequences throughout the human genome.

Our POC Molecule **HER2-205** targlets a polypurine sequence in the HER2 gene. We and demonstrated in vitro and in vivo that: 1. Level of induced DNAdamage correlates with gene copynumber: 2. Increase in apoptosis is proportional to an increase in HER2 gene copynumber; 3. Induction of apoptosis via a p53-indlependent apoptotic pathway: 4. HER2-205 treatment has performed on par with Herceptin in human breast tumor xenografls; 5. HER2-205 is a feasible therapeutic alternative for drug resistant breast and ovarian cancers with copynumber gains.

We are currently working on developing and testing D1O deliverymetlhods.



HER2-positive Breast Cancer Model



IP status: US9587238B1 Issued 3/20/2017. Pending: US20200190211A1; US 16/683.205

References: Kaushik Tiwari, M *et al.*, ***Nature Biotechnology.*** **40.** 325-334. 2022.

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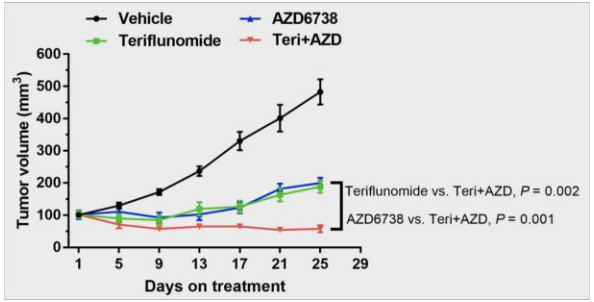
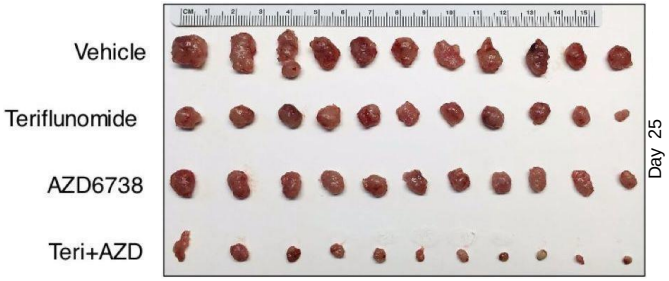
YV7358: Targeting of ARID1A-deficient cancers by exploiting a newly identified metabolic vulnerability

Principal Investigator: Gloria-Huang

- Driver mutations of the ARID1A gene are common in gynecological cancers (~35-55% of endometrial and non-serous ovarian cancers)
- Dr. Gloria Huang's lab at Yale discovered that ARID1Amutated cancers are hypersensitive to inhibitors of de novo pyrimidine synthesis, which suppress proliferation and induce DNA damage in ARID1Amutated cancer cells
- Pyrimidine synthesis inhibitors (e.g., teriflunomide) and DNA damage repair inhibitors (e.g. ATR inhibitors) are potently synergistic and selectively target ARID1A-mutated cancers
- Combination treatment with inhibitors of pyrimidine synthesis and DNA damage repair induces tumor regression in patient-derived xenograft (PDX) models of ARID1A-mutated human cancer
- **Intellectual Property:** US Patent application pending
- **Reference:** Manuscript in preparation





Figures show ing the effect of a novel combination treatment for ARID1A-mutated cancers. Mice w ere implanted w ith patient-derived xenografts from a patient w ith ARID1A-mutated ovarian cancer. After PDX establishment, animals w ere treatedwith 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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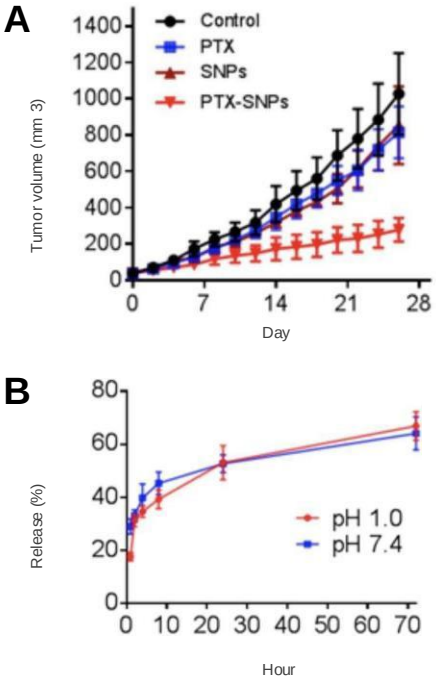
YV7119: Nanomaterial Technology to Enable Efficient Oral Drug Delivery

PARTNERED

Principal Investigator: Jiangbing Zhou

- Supramolecular nanoparticles (SNPs) that effectively enhance the oral bioavailability of cargo drugs
- Functional nano- or microstructures from five classes of MNPs and their synthetic analogs and derivatives are stable in strong acidic environment (as low as pH 1.0) and can effectively penetrate the gastrointestinal tract;
- Small compound chemotherapeutic agents and peptide therapeutics encapsulated therein show a muchgreater plasma concentration and targeted tissue adsorption following oral administration and strong efficacy in treating tumors, diabetes, and stroke in animal models.
- **Intellectual Property:** US Patent Issued



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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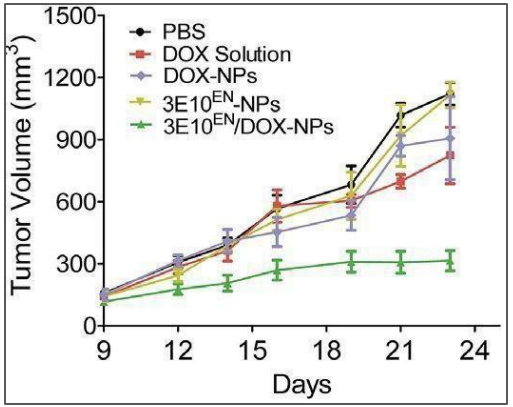
YV7013: Anti-DNA Antibody for Targeted Delivery to Tumors

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.** Provisional patent application filed
- **Reference:** Chen et al. (2016) Oncotarget



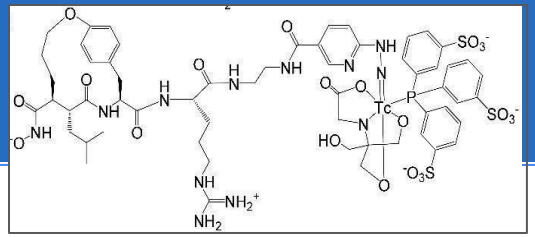
Synthesized DOX-loaded PLGA nanoparticles with surface conjugated 3E10EN have a significantly greater effect on tumors than DOX-NPs or DOX alone.

YV6966: MMP-based Inhibitors and Tracers

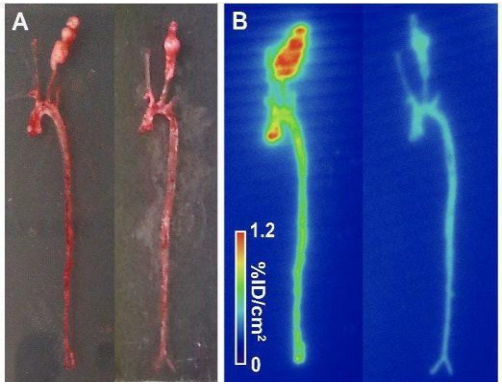
Principal Investigator: Mehran Sadeghi, PhD

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.
- Currently there 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:** PCT/US2017/026610



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



^{99m}Tc-RYM1 imaging of carotid aneurysm

Ex-vivo photography (A) and autoradiography (B) of aortae and carotid arteries from apoE-/- mice w ith CaCl2-induced carotid aneurysm injected w ith99mTc-RYM1 w ithout (left) andw iththe pre-injectionof an excessof MMP inhibitor, RYM(right).

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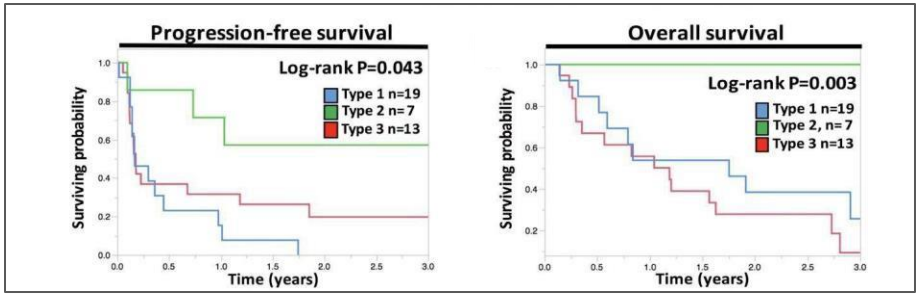
YALE VENTURES

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.
- **Intellectual Property**



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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YV6901A: A Novel piRNA-based Drug Candidate for treating Hepatocellular Carcinoma (HCC)

Principal Investigator: YongZhu, Ph.D.

PIWI-interacting RNAs (piRNAs), a class of small noncoding RNAs, stabilize the genome at transcriptional and post-transcriptional levels. We identified and tested a number of tissue and cancer-type specific piRNAs as potential therapeutic candidates.

We profiled the expression of >23,000 piRNAs in the liver tissue and identified piRNAs that are under- or over-expressed in liver cancer relative to normal liver tissue (red dots in Fig.1A). We have demonstrated anti-cancer effects of down-regulated **piR-37213-L01** both in vitro (cell proliferation, and colony formation) (Figure 1) and in-vivo (xenograft mouse models in Figure 2). **The anti-cancer effect of piR-37213-L01** was **highly specific for liver** cancer and had no effect on other cancer types tested (breast, lung, glioma, prostate, etc.). Work invloving testing **piR-37213-L01** in PDX mouse models and uncovering the mehanism of action is under w ay.

IP status: PCT/US17/19741 (50+ specific piRNA sequences for several cancer types).

References: Fu et al. 2015; Jacobs et al. 2016, Jacobs et al. 2018

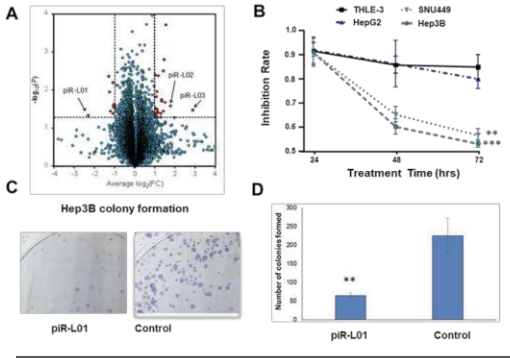

Figure 1. Identification of tumor suppressing piRNAs in HCC. **A.** Underexpressed piRNAs in the HCC tissue identified by array-based piRNA expression profiling. **B.** Restoration of piR-37213-L01 inhibits (>50%) growth of HCC cell lines. **C & D.** 70% reduced colonies formed in piR-37213-L01 treated Hep3B cells.

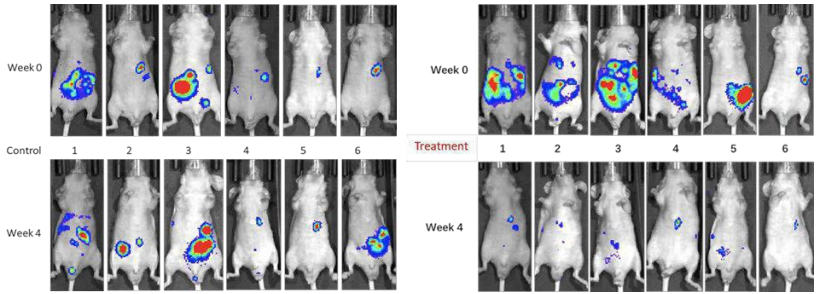

Figure 2. In vivo anticancer efficacy of LNP-piR-37213-L01 via systematic delivery. Lipid nanoparticles (LNP) was successfully used to systemically deliver piR-L01 to liver cancer cells via tail vein injection. Mice were treated twice a week for 4 consecutive weeks. Tumor signals are significantly reduced (>90%, P<0.001) after 4-week treatment.

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YALE VENTURES

YV6901B: A Novel piRNA-based Drug Candidate to Treat Glioblastoma Multiforme (GBM)

Principal Investigator: YongZhu, Ph.D.

PIWI-interacting RNAs (piRNAs), a class of small noncoding RNAs, stabilize the genome at transcriptional and post-transcriptional levels. We identified and tested a number of tissue and cancer-type specific piRNAs as potential therapeutic candidates.

We profiled the expression of >23,000 piRNAs in the glioma and normal brain tissues and demonstrated anti-cancer effects of down-regulated **piR-8041** both in vitro (cell proliferation, and colonyformation) (Figure 1) and in-vivo (xenograft mouse models in Figure 2). The **anti-cancer effect of piR-8041-L01 was highly specificfor GBM cancer** andhadno effect on other cancer types tested (breast, lung, liver, prostate, etc.). Functional analyses suggested that piR-8041 reduces cell proliferation primarilyvia induction of cell cycle arrest at the G1/S checkpoint, as wellas induction of apoptosis.

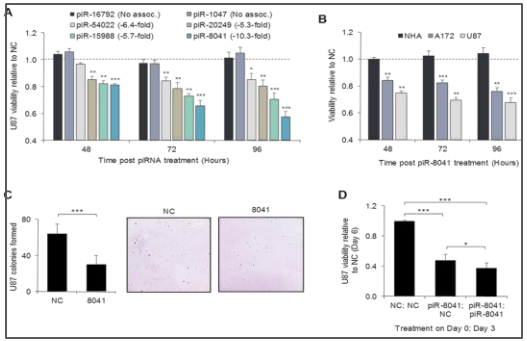

Figure 1. Anti-GBMeffect of piR-8041 in vitro. **A)** U87 cell proliferation following transfection of piRNAs underexpressed. **B)** NHA, A172, and U87 cell proliferation following piR-8041 upregulation. **C)** U87 colonies formed in soft agar 21 days after piR-8041 or NC transfection. **D)** U87 cell viability at six days following one (day 0 only) or tw o (day 0 and day 3) piR-8041 treatments.

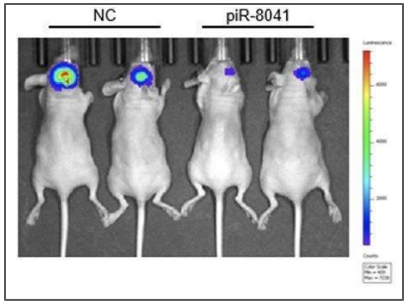

Figure 2. piR-8041 reduces tumor growthby ~50%. Images of representative mice fromeach treatment groupon day 10 after tumor implantation.

IP status: PCT/US17/19741 (50+ specific piRNA sequences for several cancer types).
References: Fu et al. 2015; Jacobs et al. 2016, Jacobs et al. 2018

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YV6886: Novel Cancer Biomarker and Target

N6-mA levels are significantly increased in aggressive forms of cancer, making it a novel therapeutic target and a powerful diagnostic marker.

- Dr. Xiao's lab at Yale is developing chemical inhibitors against methyltransferases and readers of N6-mA and testing these inhibitors in biochemical assays and patient derived xenograft (PDX) mouse models.
- Several lead compounds have been identified. Medicinal chemistry optimization and large scale screen is in progress.

Intellectual Property: US Patent Issued

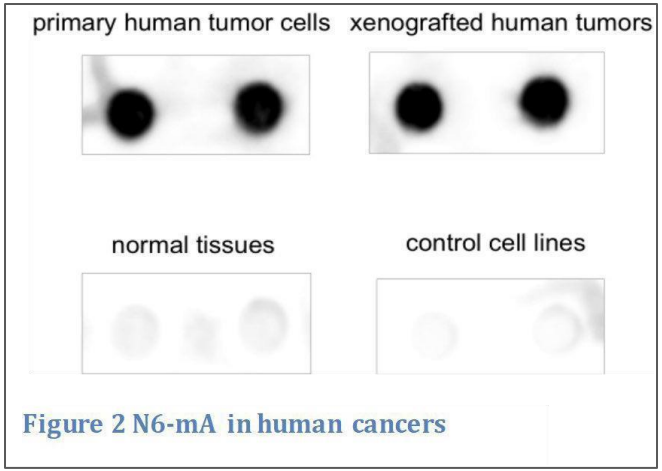

Figure 2 N6-mA in human cancers

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

Principal Investigator: William Jorgensen

Structure-based design of MIF Antagonists

MIF: Macrophage migration Inhibitory Factor is a pro-inflammatory cytokine

Clinically Validated Target: anti-MIF antibodies & MIF KO's have in vivo activity in multiple cancer and inflammatory indications

- cancer (e.g., prostate, colon, lung, melanoma)
- rheumatoid arthritis, sepsis, atherosclerosis, asthma, and ARDS

Two Diverse Highly Potent Series by Design (a):

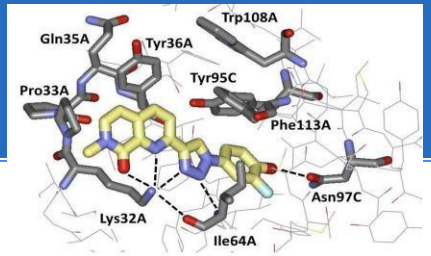
- SAR Yield: ~400 compounds, low-nM MIF-binding
- ~1000x more potent than others' antagonists

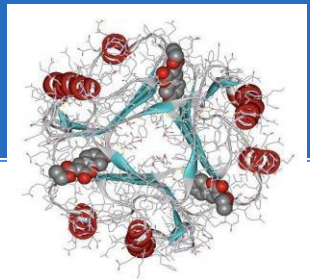
Commercial: both series are drug-like with economical synthesis routes

Hit Profiling and CYP450s: clean/excellent metabolic stability

Biologically Active (b): PC3 prostate cancer cells

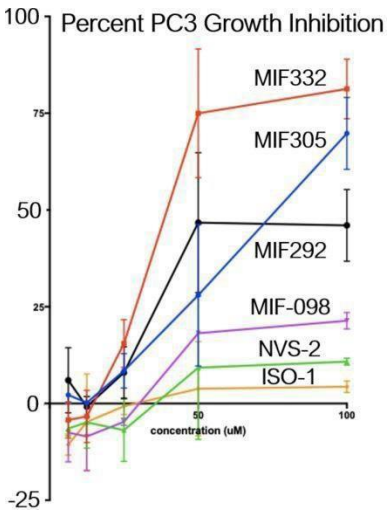
Patent Families

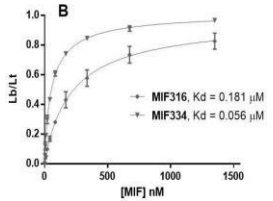




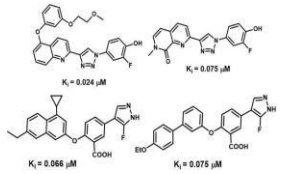
(a) Structure-based design with validated target

(b)





Novel/Improved Assays for SAR



Potent/Drug-like Leads

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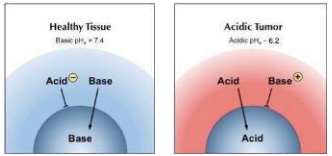
YALE VENTURES

YV6455: Targeted Therapy to Solid Tumors

Principal Investigator: John Deacon

Tumor **A**ctivated **P**ermeability (**TAP**) Therapy is a small molecule platform targeting drug delivery to all solid tumors via a universal property of solid tumors: Acidity.

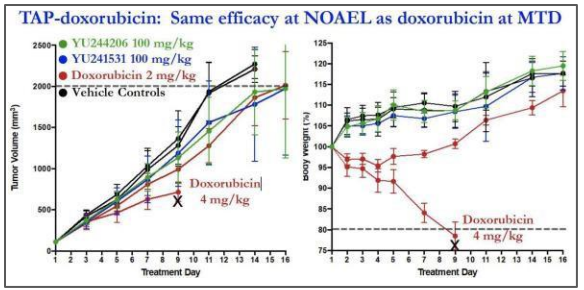


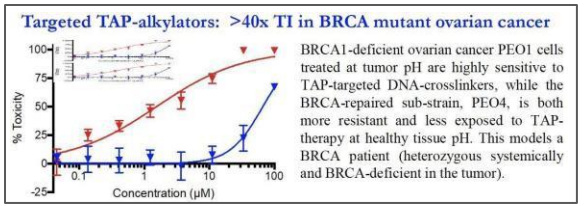
Bases target healthy cells

Acids target solid tumors

pH affects cell permeability of weakly-ionic drugs

- Tumor acidity shown to be far stronger than previously accepted, via improved pH probes
- Acidity universal in solid tumors, 95% of cancers
- The TAP platform uses a medicinal chemistry strategy to control drug distribution, targeting tumors and preventing uptake in healthy tissues
- Library of novel weak acid moieties with pK_A tuned to titrate between tumor and healthy pH
- Improves the drug's therapeutic index
- Applicable to most small molecule drugs
- IP remains unpublished, provisional patents filed





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YALE VENTURES

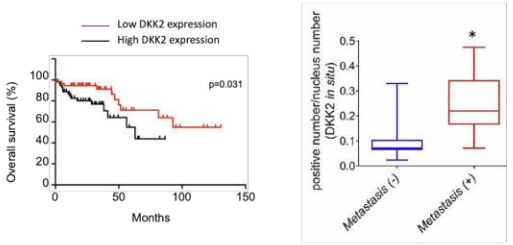
YV6325: Humanized Anti-DKK2 Clinical Candidates for Colorectal Cancer

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

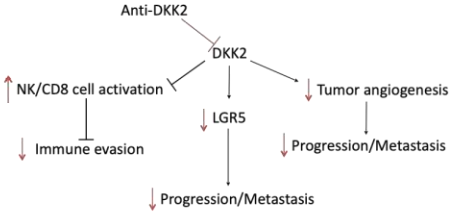
A

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

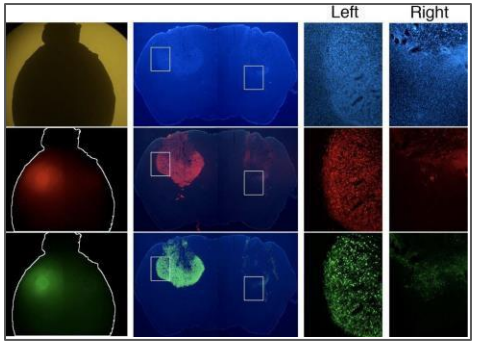
YV6290: An Oncolytic Virus for Treatment of Brain Cancers

PARTNERED

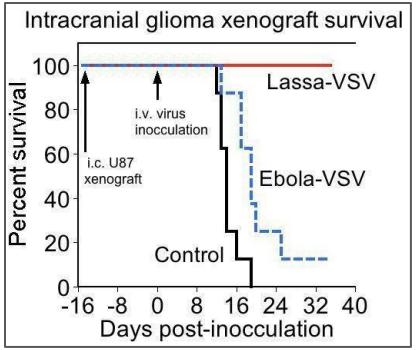
Principal Investigator: Tony Van Den Pol

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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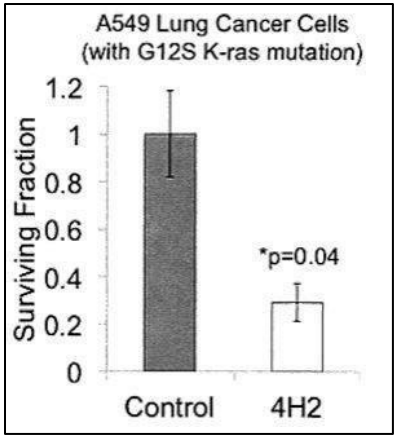
YALE VENTURES

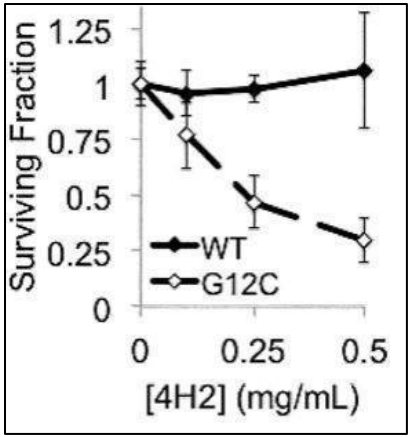
YV6265: Cell Penetrating Anti-Guanosine Antibody Therapeutic for Cancer with RasMutations

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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YV6196; 7509: Targeted Therapeutics for Cancers With Gene Amplification

Principal Investigator: Faye Rogers, Ph.D.

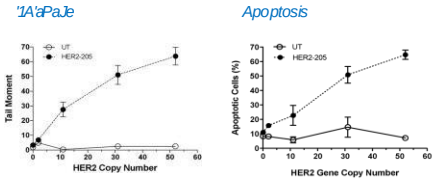
Gene amplification is a critical factor driving major oncogenic processes**.** Major drug breakthroughs in oncology such as Herceptin, Gifetinib, target the proteins encoded by amplified genes. **The problems** with the current approach: 1. Protein overexpression is a requisite for drug activity;

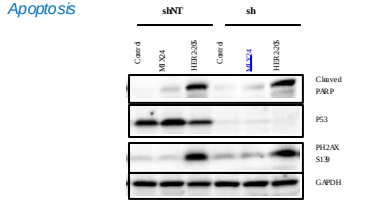
2. Many proteins are undruggable by small molecule drugs; 3. Prone to the primary and/or acquired drug resistance.
Our approach is to directly target the amplified DNA and manipulate the DNA damage response to **trigger apoptosis in cancer cells.** We developed damage-inducing oligonucleotides (DIOs) that directly convert amplified oncogenes to excessive DNA damage and activate apoptosis in cancer cells. DIOs **target** specific polypurinesites in the amplified cancer genes. **Mechanism of Action**: sequence-specific gene targeting and DNA damage to induce p53-independent apoptosis in cancer cells.

DIO advantages: 1. Hijacking cell's own machinery, 2. Reduces normal tissue toxicity and off-target effects, 3. Independent of protein cellular function; 4. Multiple cancer types can be targeted with our DIO approach: 461 amplified genes; 14 cancer subtypes; 519, 971 unique DIO targeting sequences throughout the human genome.

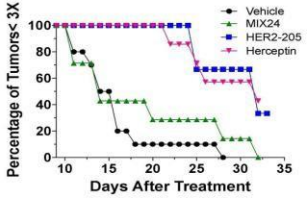
Our POC Molecule HER2-205 targets a polypurine sequence in the HER2 gene. We and demonstrated in vitro and in vivo that: 1. Level of induced DNAdamage correlates with gene copynumber; 2. Increase in apoptosis is proportional to an increase in HER2 gene copynumber; 3. Induction of apoptosis via a p53-independent apoptotic pathway; 4. HER2-205 treatment has performed on par with Herceptin in human breast tumor xenografts; 5. HER2-205 is a feasible therapeutic alternative for drug resistant breast and ovarian cancers with copynumber gains.

We are currently working on developing and testing DIO delivery methods.





HER2-positiveBreast CancerModel



IP status: US9587238B1 Issued 3/20/2017. Pending: US 20200190211A1; US 16/683,205

References: Kaushik Tiwari, M*et al.*, ***Nature Biotechnology***, **40**, 325-334, 2022.

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YALE VENTURES

YV6056: RNA Hairpin Molecules as Immunooncology Agents

PARTNERED

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

A short hairpin RNA, alone or in combination with anti-PD1 therapy, activates Rig-I and stimulates immune response

- Stem Loop RNA 14 (SLR14) induces interferon production as a RIG-I agonist.
- Efficacy demonstrated in mouse in vivo tumor models.
- Combination augments efficacy of anti PD-1 therapy.
- Has abscopal and memory effects.

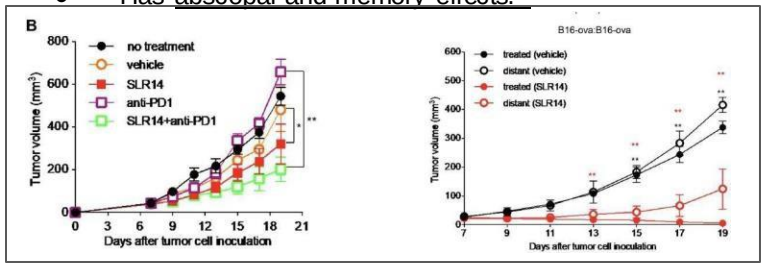
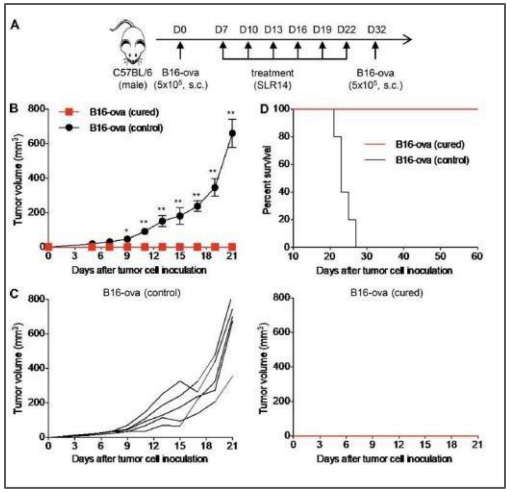


Figure 1. Combination treatment with SLR14 and anti-PD1 leads to better antitumor effects than single treatment. Average tumor volume for each group of YMR1.7-bearing mice.

Figure 2. SLR14 i.t. treatment induces an effective abscopal effect. Bilateral B16-ova:B16-ova tumor model

Figure 3. B16-ova–cured mice after SLR14 treatment develop immune memory.



IP status: US62/743369, US2016/0046942, WO2014159990

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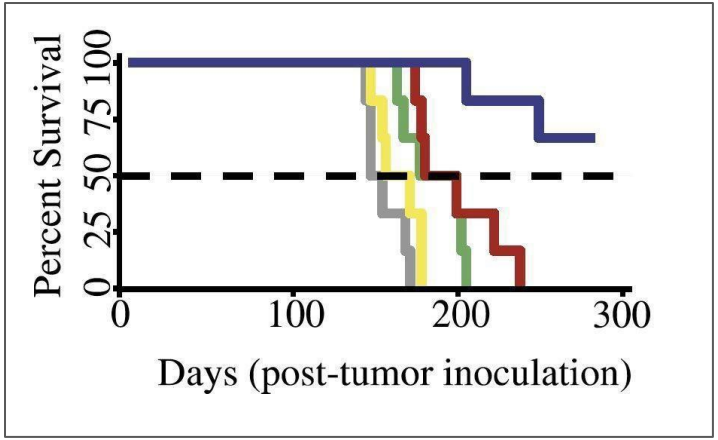
YALE VENTURES

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; Ediriwickremaet et al., 2014 Biomaterials; Gaudin et al., 2016 Biomaterials; Saucier-Sawyer et al., 2016 J Control Release.
- **Patents Applications:** 20150118311; 20140371712

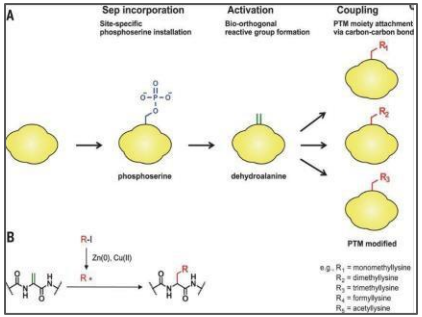


Kaplan-Meier survival curves for tumor-bearing rats: blue line, brain-penetrating paclitaxel NPs (median survival 46 d); red line, standard paclitaxel NPs (mediansurvival 38 d); green line, free paclitaxel (median survival 30 d); yellow line, blank NPs (median survival 31 d); grey line, no treatment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

YV5714: Antibody Engineering - ADCs

Principal Investigator: Dieter Söll

- Selenocysteine (Sec) Method
  - Therapeutic Utility
    - ADC & Rx proteins with novel properties & compositions
    - Rapid Purification via Sec
    - 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" modification



Yang et al (2016) Science 354, 623

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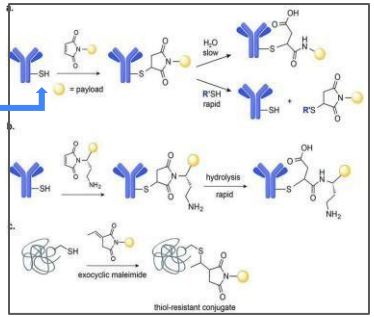

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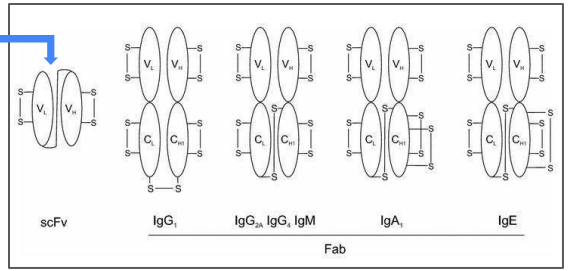


Systematic screening of soluble expression of antibody fragments in the cytoplasm of E. coli

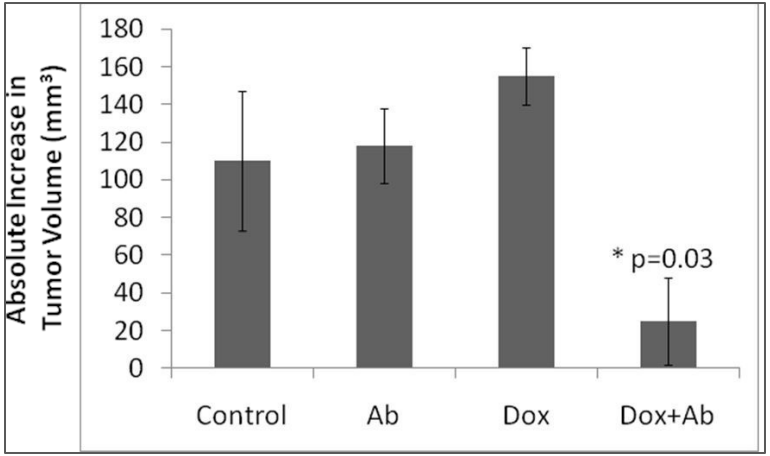
Anna Gaciarz, Johanna Veijola, Yuko Uchida, Mirva J. Saaranen, Chunguang Wang, Sohvi Horkko and Lloyd W. Ruddock

YV5478: Antibody Therapeutic for Cancer

PARTNERED

Principal Investigator: James Hansen, Peter Glazer

- Antibodies currently approved for cancer therapy lack the ability to directly penetrate into cells.
- **3e10** is a cell-penetrating anti-DNA antibody with clinical data for another indication that has been identified as a therapeutic for the treatment of cancer.
- Active as a single agent against tumors with deficits in DNA repair, e.g. BRCA mutations
- Significantly enhances sensitivity to DNA-damaging therapies (e.g. radiation, doxorubicin).



As shownabove, a mouse xenograft model using U87 humanglioma cells demonstrate that the cell-penetrating antibodysynergizes with doxorubicinin vivo.

IP status: PCT/US2015/047174 filed

References:

Weisbart et al., 2015, Sci Rep

Hansen et al., 2012, Sci Transl Med

Yale

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YV5120: Universal Cancer Vaccine candidate

Principal Investigator: Madhav Dhodapkar

Immunogenic Epitopes as Targets for Universal Cancer Vaccines

- Unlike other vaccine-based technologies, YV5120 is not cancer-type specific, but a “panvaccine” antigenopportunity
- The human immune system can respond to YV5120 and identify the specific immunogenic epitopes derived from the YV5120 antigen (see figure) as a matter of surveillance rather than response.
- YV5120 target:
  - is important in self-renewal and maintenance of pluripotencyin embryonic stem cells
  - is not cancer-type specific
  - is a “pan-vaccine” antigen
- Applications:
  - universal target for a general cancer vaccine
  - YV5120-specific cellular preventive therapyfor preventing cancer-like sides effects arising from stem cellbased therapies

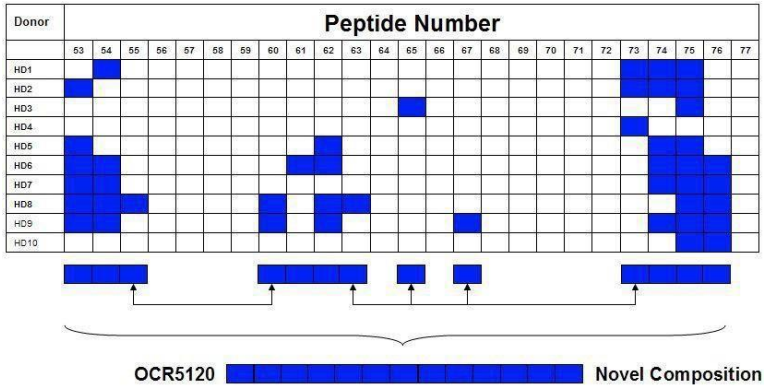


Figure 1: Map of OCR5120 immunogenic epitopes derived from human antigen isolated from patients (Short Blue) and vaccine candidate (Long Blue; OCR5120).

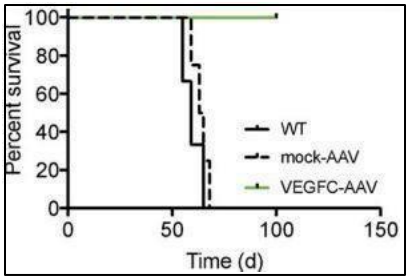
Issued US Patent

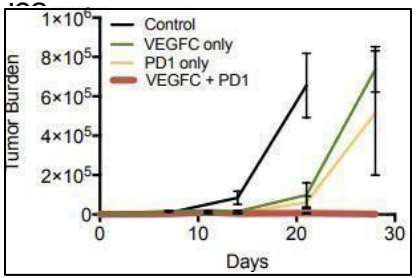
YV7502: Vascular Endothelial Growth Factor C (VEGF-C) to treat Glioblastoma (GBM)

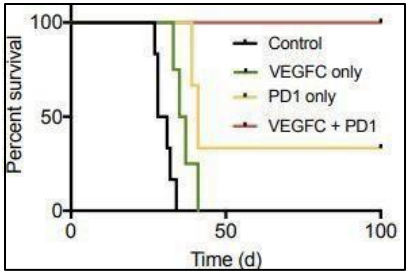
Principal Investigator: Akiko Iwasaki, Ph.D.

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 m ice







Pending Patents:
PRV filed 62/768,390, US/PCT to be filed

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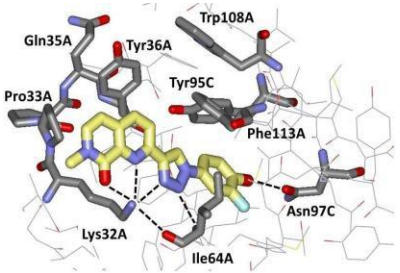
YV6558: MIF Antagonists for Oncology & Inflammation

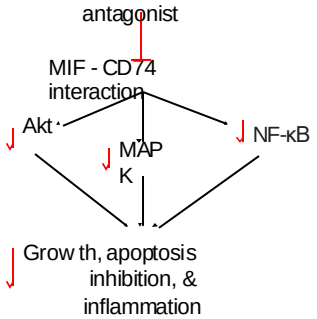
- **Background**: Macrophage migration inhibitory factor (MIF) is a pro-inflammatory cytokine
  - Implicated in multiple pathways (**B**) and a validated target for multiple indications
    - Cancer (prostate, colon, lung, melanoma, etc)
    - Inflammation (sepsis, rheumatoid arthritis, atherosclerosis)
  - Chemistry Publications
- **Assets**: Two diverse series by structure-based design (**A, C**)
  - Possible clinical candidate (MIF394) and related com
    - Long half-life (5.6 hours IV& 4.6 hours PO) (dns)
    - Drug-like (**C**) with economical synthetic routes
    - Validated biological activity in vitro (**D**) and in vivo sepsis (**E**)
    - Clean hit profiling via PanLabs (dns) and well-tolerated at 300mg/kg PO multiday mouse tox (dns)
- **IP**: Multiple patent families with issued and pending patents. MIF394 patent application in preparation

Innovator: William Jorgensen, PhD

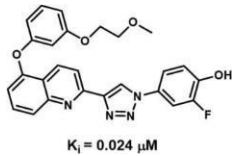
A Structure-based design



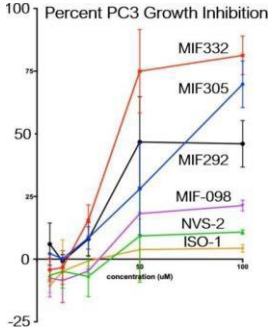
B MIF involvement in key pathways. Effects of MIF antagonists are in red.



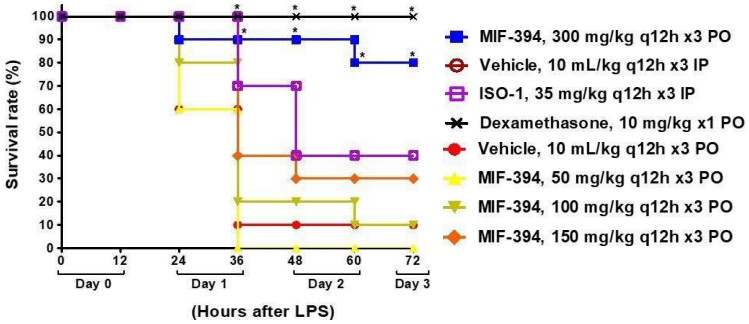
C Drug-like lead compounds.



D PC3 in vitro proliferation assays shows MIF300 Series Superiority



E Sepsis model shows dose response of MIF394



Yale Ventures Contact: David A. Lewin, PhD /

YALE VENTURES

YV8596: tRNATherapeutics for Cancer

PI: Wendy Gilbert, PhD

Background:

- Many tumors require high levels of tRNA-modifying enzymes to support increased protein synthesis

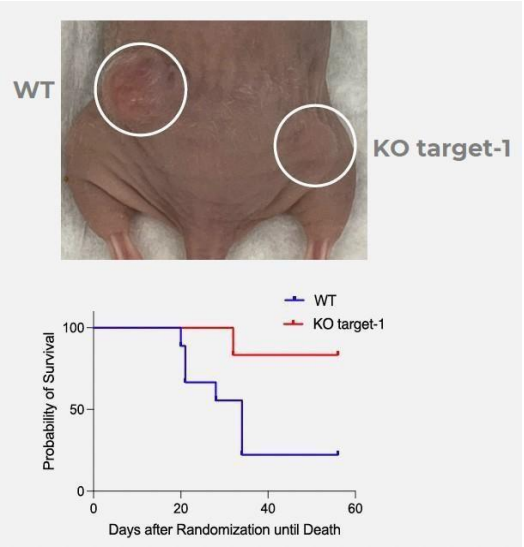
Indications: Hepatocellular carcinoma, Non-small cell lung cancer, Urothelial carcinoma of bladder, Colon adenocarcinoma, various other malignancies

Innovation & Asset: Engineered tRNA platform to inhibit tRNA-modifying enzymes

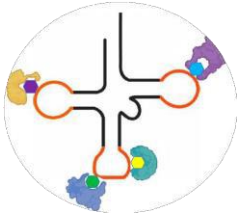
- Single tRNA can inhibit over 25 enzymes
- Highly potent - lead candidate exhibits nanomolar IC_{50}
- Flexible tRNA design can be specifically tuned for specific patient and cancer
- Increased specificity vs small-molecule inhibitors

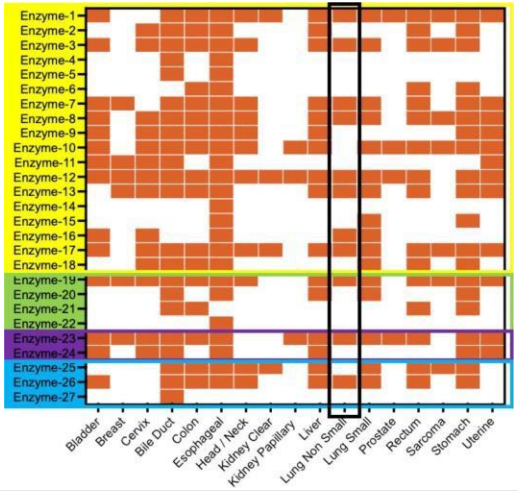
IP: Patent application pending

Below: Genetic knockout of tRNA-modifying enzyme, dihydrouridine synthase, reduces tumor volume and increases survival in mouse model of malignancy.



Right: Schematic of an engineered tRNA, which can target multiple different tRNA-modifying enzymes. Below: Various tRNA-modifying enzymes (Y-axis) are upregulated in many different cancers (X-axis). For example, non-small cell lung cancer has 11 overexpressed enzymes.





YALE VENTURES

Contact: David A. Lewin, PhD / david.lewin@yale.edu

Yale

YV8224: Human cortical organoids with engineered microglia-like cells

Principal Investigator: In-Hyun Park, PhD

Background:

- Human cortical organoids (hCOs) are valuable models of 3D tissue, but their potential is limited by their lack of mesenchymal components, namely microglia

Indications: Glioblastoma Multiforme (treatment); neurodegenerative & neurodevelopmental disorders (model platform)

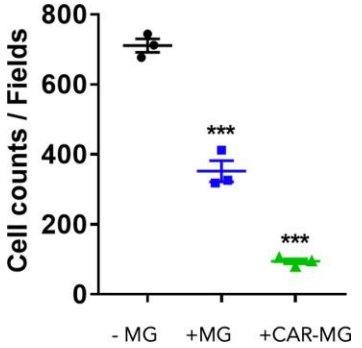
Innovation & Asset: Novel platform to develop microglia-containing hCOs using human embryonic stem cells:

- Tunable, efficient method of microglia generation (Nature publication)
- Microglia may be modified with chimeric antigen receptors (CAR) and used as immunotherapy (A)
- hCOs with microglia allow for improved investigation of numerous brain diseases, including Alzheimer's (B), autism, and schizophrenia

IP: Patent Application Pending

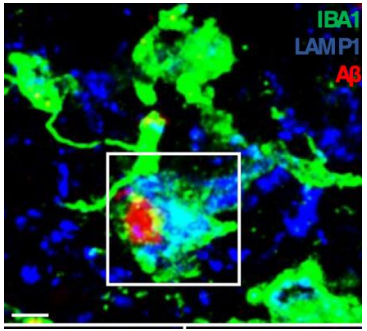
A

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

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.

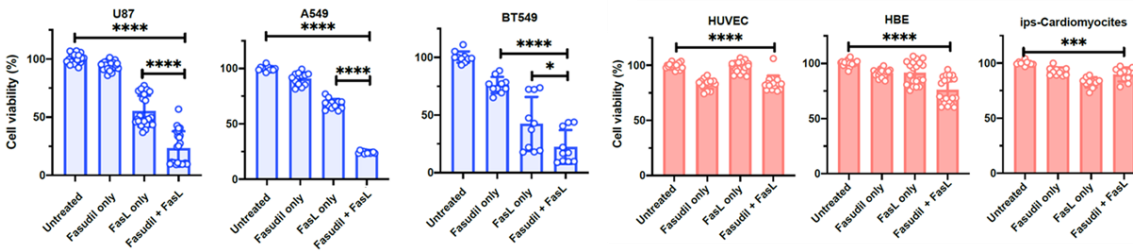
Indications: Anti-tumor drug combination that spares non-cancerous cells.

Innovation & Asset: Sensitization of tumor cells to Fas ligand by increasing the number of receptors on the cell surface via changing intra-cellular mechanical tension.

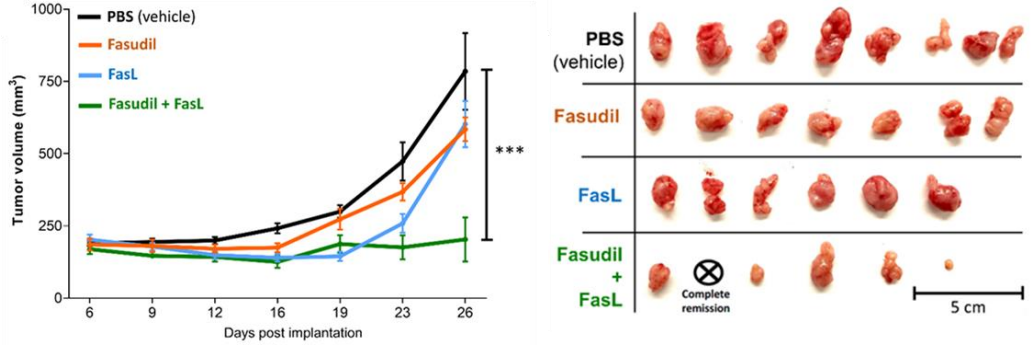
- Strong in vitro cytotoxicity was demonstrated in multiple cancer lines: Glioblastoma, triply-negative breast, lung, prostate, and liver cancer.
- Has milder effect on non-cancerous cells: Cardiomyocytes, endothelial cells and bronchial epithelial cells are spared.
- Showed potent in vivo tumor inhibition in a xenograft glioblastoma model in nude mice.
- Potential alternative to chemotherapy with milder side effects.
- **IP:** Patent application pending

Innovators: Mehmet Kural, PhD and Laura Niklason MD, PhD

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.



YALE VENTURES

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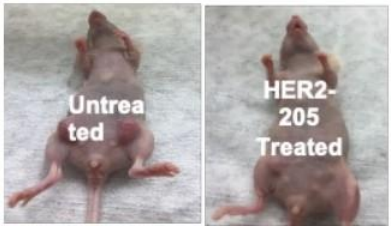
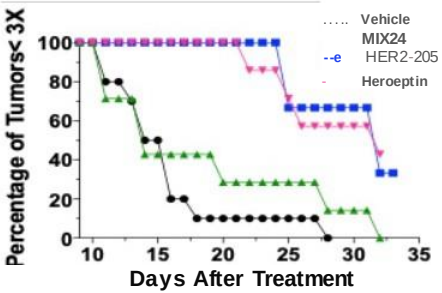
Yale

YV 6196; 7509: Targeted Apoptosis by sequence-specific DIOs for Cancer Treatment

Background:
Gene amplification drives major oncogenic processes. Herceptin and work by targeting the overexpressed proteins encoded by amplified genes. However, targeting proteins has many drawbacks (undruggable targets, drug resistance, etc.).

Innovation:
We can design damage-inducing oligonucleotides (DIOs) that directly bind specific . - r i c h sites in amplified oncogenes and induce excessive DNA damage. Multiple cancer types can be targeted with our DIO approach: there are 461 amplified genes in 14 cancer subtypes. We can potentially design 519,971 unique DIOs to target specific sequences throughout the human genome. This new approach can be used as a platform for developing targeted treatments in many different cancers with gene amplification.





Our POC Molecule HER2-205 targets a sequence in the HER2 gene. In vitro and in vivo, we demonstrated that: 1. Level of induced DNA damage correlates with ith gene copy number; 2. The increase in apoptosis is proportional to the increase in HER2 gene copy number; 3. Induction of apoptosis via a p53-independent apoptotic pathway; 4. HER2-205 treatment has performed on par with Herceptin in human breast tumor xenografts; 5. HER2-205 is a feasible therapeutic alternative for drug-resistant breast and ovarian cancers with copy number gains. We are currently working on developing and testing DIO delivery methods.

IP status: US958723881 Issued 3/20/2017. Pending: US 20200190211A1; US 16/683,205
References: Kaushik Tiwari, *Met al.*, ***Nature Biotechnology*, 40,** 325-334, 2022.

Neuroscience and Visual Science

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 cognitive deficits caused by FG7142 with a low dose of the selective β1-AR antagonist, betaxolol (Beta, 0.001-0.1 mg/kg),

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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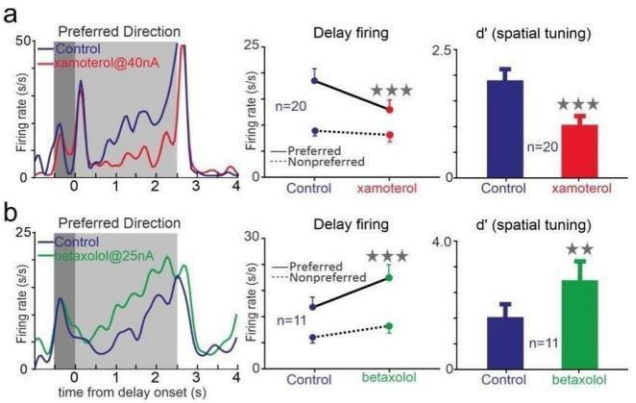
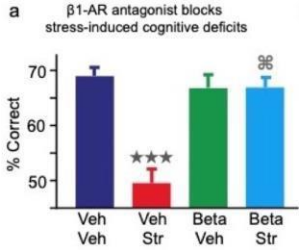
IP status: US Appl 63/424,811





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.

Yale

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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)

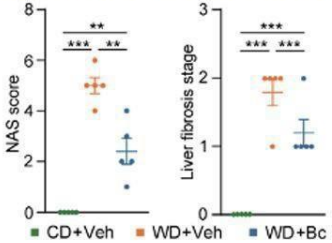
Indications: NASH, fibrosis, anorexia, depression, endometriosis

Innovation & Asset: Small-molecule Bobcat339 (Bc) degrades TET3 protein

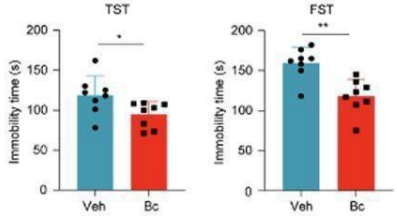
- Decreases NASH/fibrosis (A) and depressive behaviors (B)
- Improves appetite (C) and body weight (D) in an activity-based mouse anorexia model
- No toxicity, well-tolerated

IP: Patent application pending

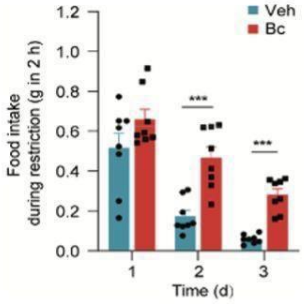
A Mice treated with Bc had decreased NFLD activity score (NAS) and fibrosis stage. WD, a western diet used to induce NASH.



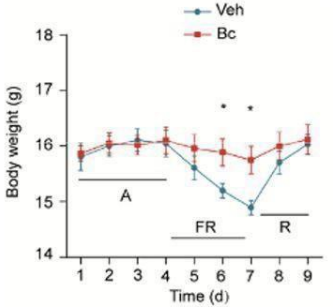
B Mice treated with Bc had improved performance on tail suspension test (TST) and forced swim test (FST), which evaluate the impact of depression on behavior



C Mice treated with Bc had increased food intake during the food-restriction (FR) period



D Mice treated with Bc maintained normal weight during the FR period



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YV8216: Axon Spheroid-induced CNS Disorders

Principal Investigator: Jaime Grutzendler, MD

Pathological Neuronal Branching: Plaque-Associated Axonal Spheroids (PAAS)

- Axon Conduction Disorders
- Standard of Care: Alzheimer's Disease
- Novelty: no therapeutics target PAAS or axon conduction
- In Vivo Model: mouse model recapitulates PAAS pathology of human post-mortem brain samples (Fig. 1)
- Axonal Spheroid Induced Target: 1) enzyme
  - Target 2: plasma membrane integral protein
- Intervention Strategies: small molecules, siRNA/antisense, antibody, PROTACS
- In Vivo Assessment of Efficacy: brain interhemispheric axonal conduction

Validity of Therapeutic Hypothesis

- Human/Mouse: human and mouse PAAS morphology (Fig.1)
- Mouse: diminished PAAS (observed) results in normalization of axonal conductance (two targets, two modalities; Fig.2a Target 1/ Fig.2b: Target 2)

Anticipated Clinical Assessment of Efficacy of PAAS-directed Therapy

- Neuropsychological and computer-assisted measurements of cognitive processing speed/reaction times.

IP: Patents Pending
Related: YV8237

Fig.1

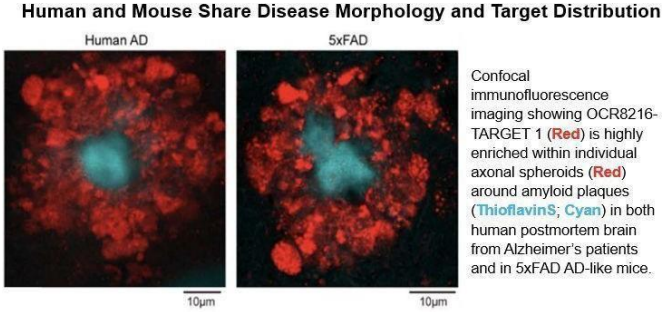


Fig. 2a

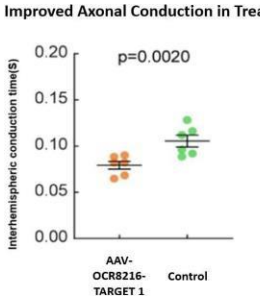
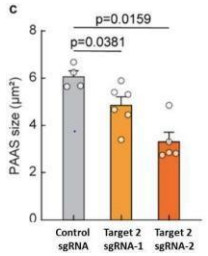


Fig. 2b



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YV8216: Targeting Axonal Spheroids in Alzheimer's Disease

Principal Investigator: Jaime Grutzendler, MD

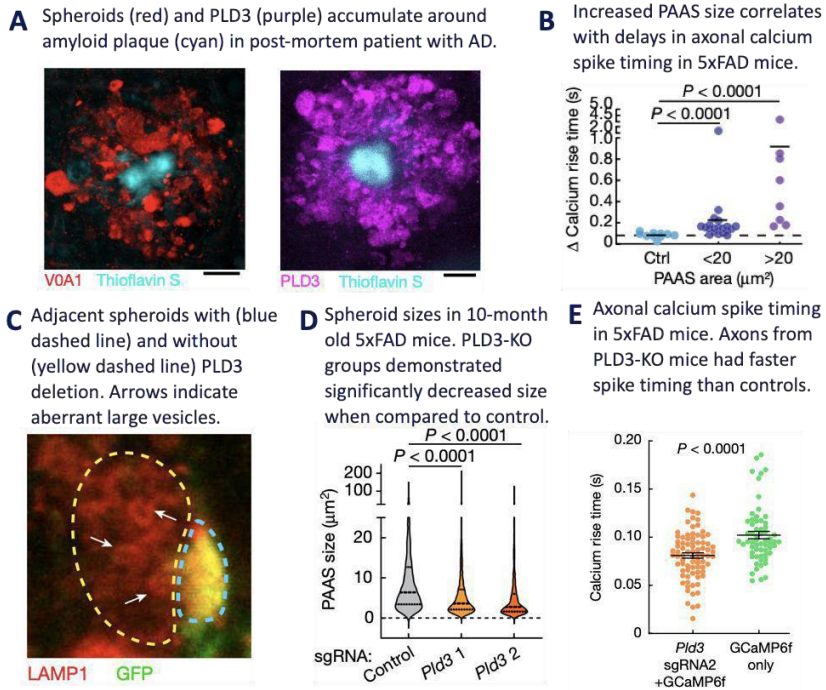
Background: Plaque-Associated Axonal Spheroids (PAAS)

- 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



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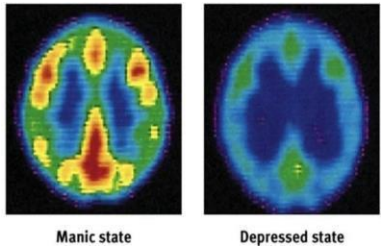
YALE VENTURES

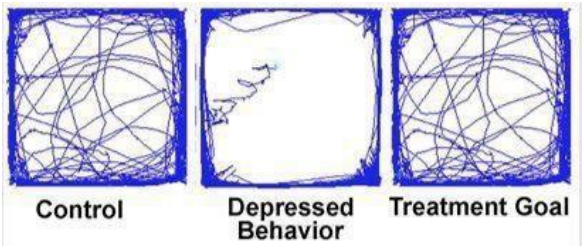
YV7709: Novel Druggable Target to Treat Bipolar Disease

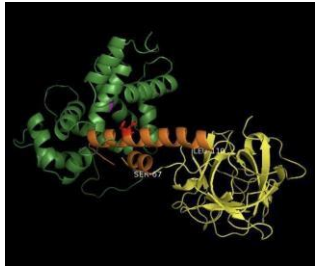
Principal Investigator: Barbara Ehrlich

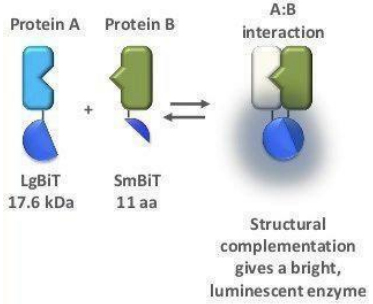
- 6 million adults in US have BP
  - severe mood swings
  - 1 in 5 commits suicide
- All available BP drugs: toxic, poor efficacy, or both
- Current trials lack novel compounds, mainly drug combinations
- YV5570 target levels affected in bipolar
  - Target structures + hits known
  - Screenable/Structure-based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

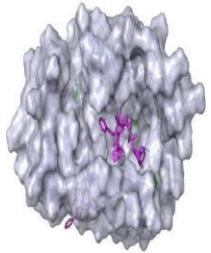


Baxter and Phelps, UCLA









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YV7541: RABET™ Platform: Retinal and Brain Endothelial Targeting

Principal Investigator: Jaime Grutzendler, MD

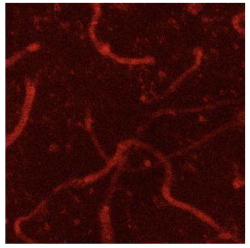
RABET™ Background:
- Broad platform applicability: eye and brain indications
- RABET™ is the first precision targeting platformfor endothelial cells
- RABET™ molecules are small, highly specific, orally bioavailable & inherently fluorescent

RABET™-Rx Conjugates and Platform Characterization& Features
- MoA of targeting/delivery understood and characterized
- MoA preserved across preclinically-relevant species and humans
- RABET™-Rx molecules have been tested and/or designed
- The RABET™ platformis chemically flexible and conjugation tolerant

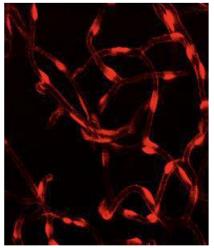
RABET™ Platform: Key Findings/Characteristics
- Oral Bioavailability demonstrated
- MoA confirmed in vitro and in vivo
- Confirmed selective cellular entry of RABET™-Rx molecules
- RABET™-Rx maximum delivered molecular w eight ~2000 Daltons (tested)
- RABET™-Rx conjugate precision and potency is preserved
- Multiple RABET™ scaffold chemotypes characterized (cytoplasmic and/or nuclear targeting)

RABET™ IP:
- RABET™ Platform compositions & methods
- RABET™-Rx compositions & methods

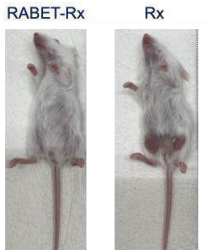
RABET™ is orally bioavailable (delivery to brain endothelium)



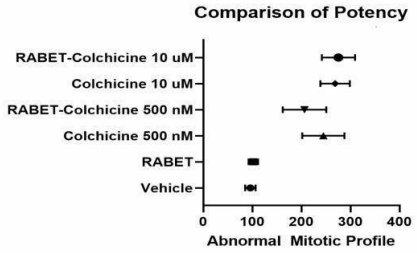
RABET-Rx retains RABET™ precision (brain endothelial cells)



RABET-Rx reduces off-target effects of Rx



RABET-Rx preserves Rx pharmacological activity



Example Indications

Retinal indications	Brain indications
Age-related macular degeneration	Vascular dementia
Diabetic retinopathy	Alzheimer's disease
Posterior uveitis	Stroke
Ischemic retinal vasculitis	Brain vasculitis
Retinopathy of prematurity	Hereditary cerebral cavernous malformations

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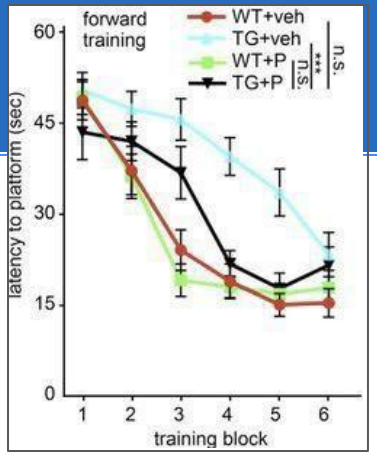
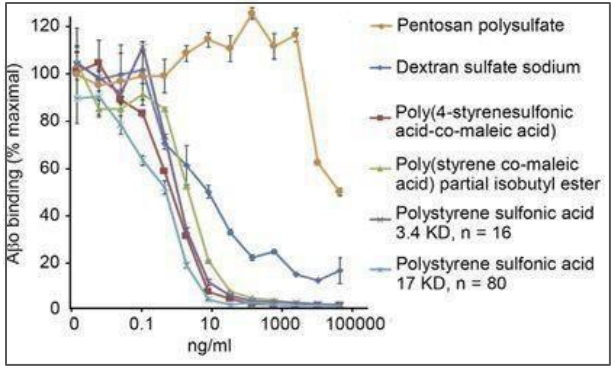
YV7470: Orally-available polymers to treat Alzheimer's Disease (AD)



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, inhibitingAβ binding
- Oral delivery of PSCMA(Polymer 3) inhibits the Aβ/PrP interaction and rescues Alzheimer's Disease-induced learning and memory deficits in mice
- **Pending Patent:** US 62/694710



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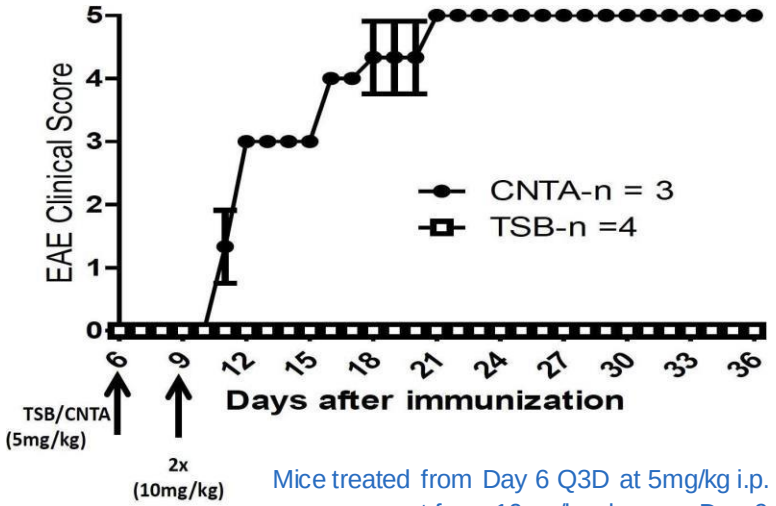
YALE VENTURES

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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YV7229, 8031: Novel Therapeutics for Treating Dry AMD

Principal Investigators: Mark Fields, Ph.D., Lucian Del Priore, M.D., Ph.D.

Age-related macular degeneration (AMD) is the leading cause of blindness in elderly patients, affecting > 8 M individuals in the US. There is no effective therapy for **90% of AMD patients with "dry" or atrophic form of AMD.** We focus on targeting oxidative stress and mitochondrial dysfunction in the retinal pigment epithelium (RPE) cells to prevent progression from the early dry AMD to the advanced forms of AMD.

Using HTS of library of ~85,000 small molecules,, we identified 3 lead compounds (RGV-001, 2, 3) for follow-up studies.

Our lead candidate RGV-001:

- Improves AMD donor-derived RPE survival and mitochondrial function
- Improves retinal thickness and reduces inflammation in BLD model
- binds BCO2 Carotenoid-cleaving dioxygenase, mitochondrial, dose-dependent way
- We successfully developed formulation for effective topical delivery (eye drops); in the process of developing intravitreal and sub-tenon formulations. .

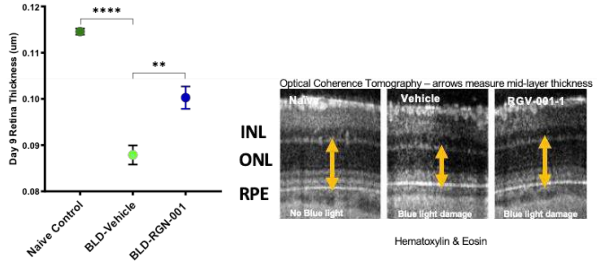
RGV-002 and RGV-003 molecules: chemically and pharmacologically distinct from RGV-001.

- Second generation with improved solubility

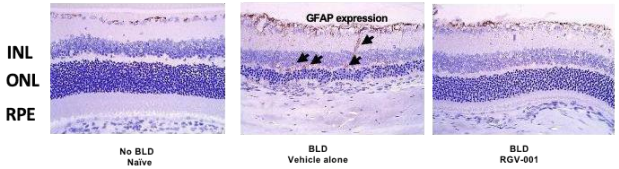
These two compounds are being developed for Retinitis Pigmentosa, Glucoma and Optic Neuropathy.

IP status: PCT/US2019/012749; US16/923,492; US63/338,264; US63/411,405 (est. exp. 2043)

RGV-001-1 improves retinal thickness in BLD model



RGV-001-1 prevents inflammation in BLD model



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YALE VENTURES

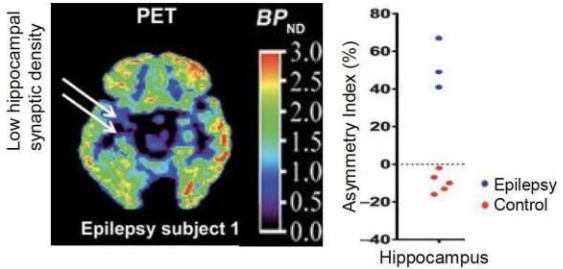
YV7160: Radiopharmaceuticals for Synaptic Imaging

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 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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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.

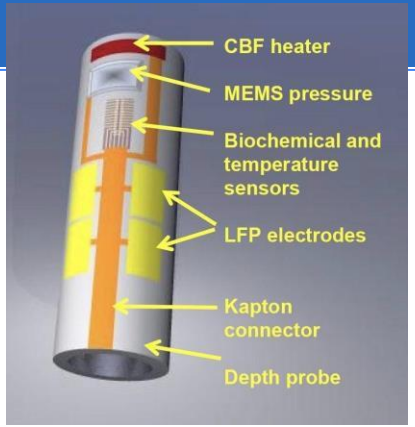

Fig 1. Intracranial pressure (icP), intracranial EEG (icEEG), intracranial temperature (icT), brain tissue oxygen (PBTO2) and cerebral blood flow (CBF)

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

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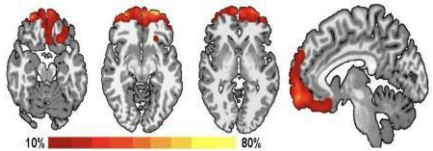
YV6980: Neurofeedback Therapy for Treatmentof OCD

Principal Investigator: Chris Pittenger, MD/PhD

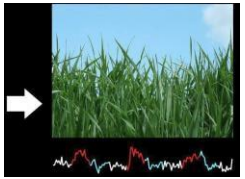
Functional near-infrared spectroscopy (fNIRS)-driven feedback for psychiatric symptoms

- 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

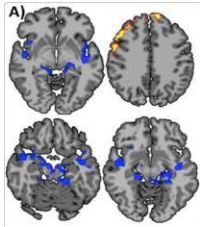
Stimuli-responsive regions of the OFC are identified in OFC patients during Neurofeedback protocol



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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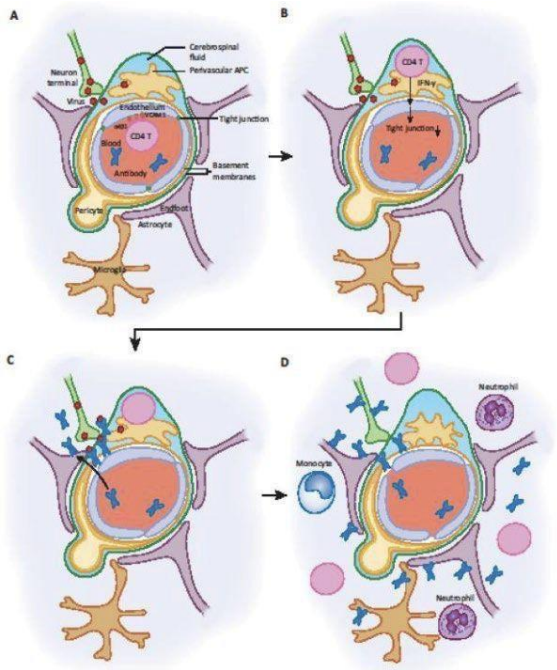
YALE VENTURES

YV6953: Antigenic peptides help antibody access to the brain

Principal Investigators: Akiko Iwasaki

- **Background:** Antigen-specific CD4+T cells that recognize cognate antigen -- presented by perivascular APCs -- secrete IFN-γ, and reduce tight junctions between ECs. Circulating antibodies can access the brain parenchyma by crossing the BBB.
- **Treatment:** Vaccine and antibody-mediated immunotherapy against neurotropic viruses and brain cancers
- **Innovation:** Foundations for future therapeutics based on enabling antibody access to the brain
- **Reference:** 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.



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YALE VENTURES

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

Principal Investigator: Amy Arnsten, PhD

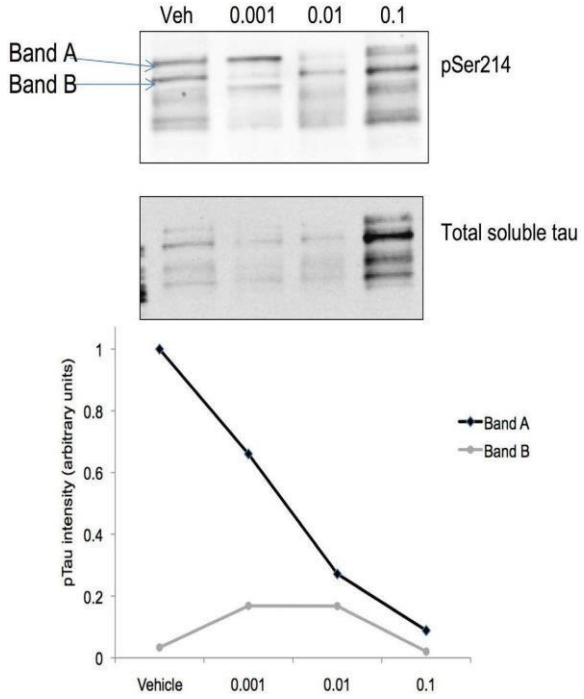
Age-related increase in phosphorylation of tau and its aggregation at the dendritic spines of the cortical pyramidal neurons results in formation of neurofibrillary tangles (NFT), eventually leading to neurodegeneration in the PFC

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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YV5708: mGluR5 Modulator For Treatment of Alzheimer's Disease

PARTNERED

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

- **Background:** mGluR5 has been identified as part of a cell-surface complex that binds to Ab oligomers, which leads to synaptic loss and
- neuronal death.
- A small molecule silent allostericmodulator (SAM) has been identified that blocks Ab binding, **but does not interfere with normal glutamate signaling.**
- Treatment of AD mice with SAMimproves memory and learning (Fig.1), and ameliorates synaptic loss (Fig.2).
- **IP status:** Extensive patent portfoliocovers novel composition of matter and is available for licensing.
- Allyx

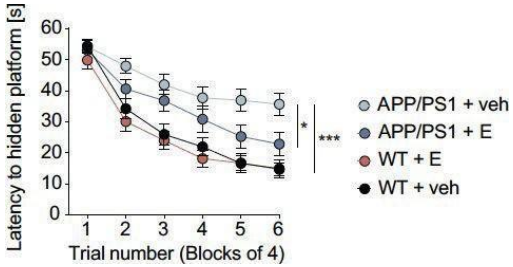


Fig. 1. SAM reverses learning and memory deficits in APP/PS1 transgenic mice after 4 weeks of treatment. Spatial learning in Morris-Water-Maze.

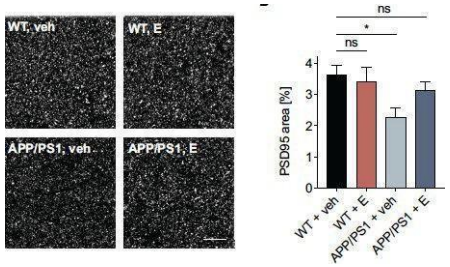


Fig.2. SAM recovers loss of synaptic markers in APP/PS1 mice after 5 weeks of treatment. PSD95 area.

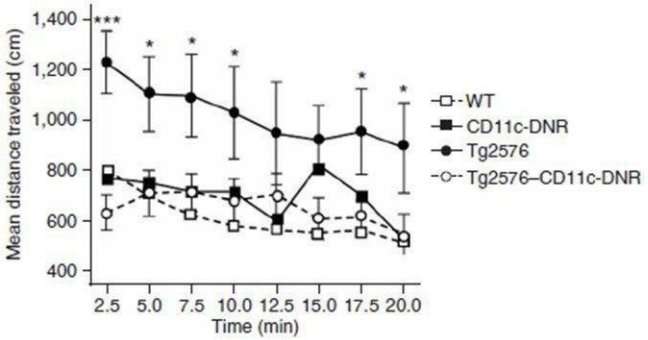
Haas et. al Cell Rep. 2017 Jul 5;20(1):76-88.

YV5007: A Novel Approach to Treating Alzheimer's disease

Principal Investigator: Richard Flavell

Treating Alzheimer's Disease by blocking TGF-β signaling

- Blocking the transforming growth factor-β (TGF-β) pathway in peripheral macrophagescan significantly clear up β-amyloid plaques in the brain.
- These results provide the basis for a novel therapeutic intervention for Alzheimer's disease by blocking the TGF-β-Smad2/3 signaling pathway in peripheral macrophages.
- Blockade of TGF-β works peripherally without the need to permeate the bloodbrain barrier to enter the brain.



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.

Intellectual Property: U.S. Patent 9,095,126

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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; option to commercially-developed human mAbs.

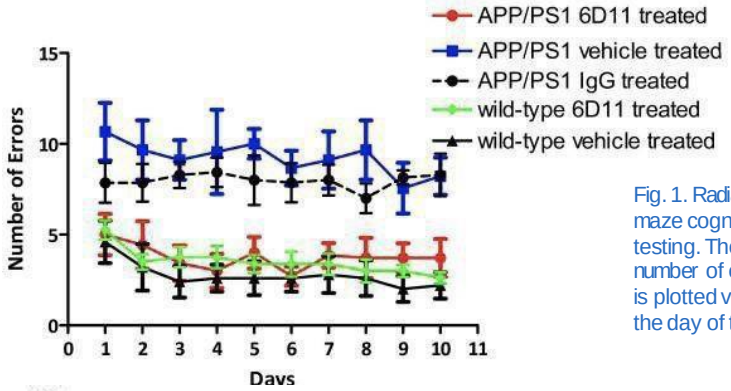

Fig. 1. Radial arm maze cognitive testing. The number of errors is plotted versus the day of testing.

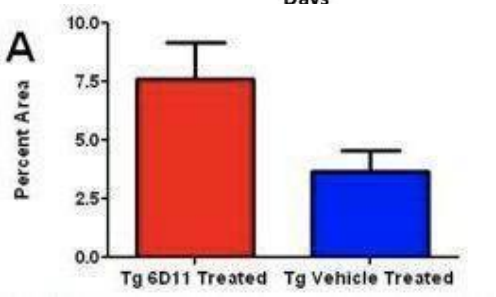

Fig. 2. Synaptophysin immunoreactive presynaptic terminals in the molecular layer of the dentate gyrus of the hippocampus.

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YV8224: Human cortical organoids with engineered microglia-like cells

Principal Investigator: In-Hyun Park, PhD

Background:

- Human cortical organoids (hCOs) are valuable models of 3D tissue, but their potential is limited by their lack of mesenchymal components, namely microglia

Indications: Glioblastoma Multiforme (treatment); neurodegenerative & neurodevelopmental disorders (model platform)

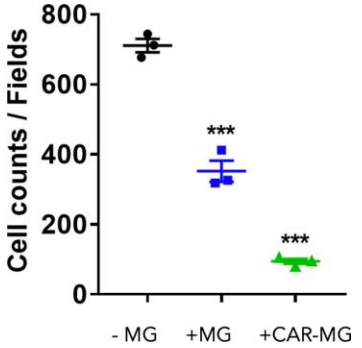
Innovation & Asset: Novel platform to develop microglia-containing hCOs using human embryonic stem cells:

- Tunable, efficient method of microglia generation (Nature publication)
- Microglia may be modified with chimeric antigen receptors (CAR) and used as immunotherapy (A)
- hCOs with microglia allow for improved investigation of numerous brain diseases, including Alzheimer's (B), autism, and schizophrenia

IP: Patent Application Pending

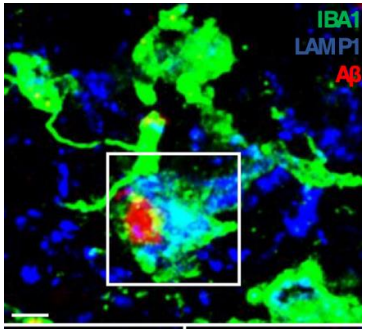
A

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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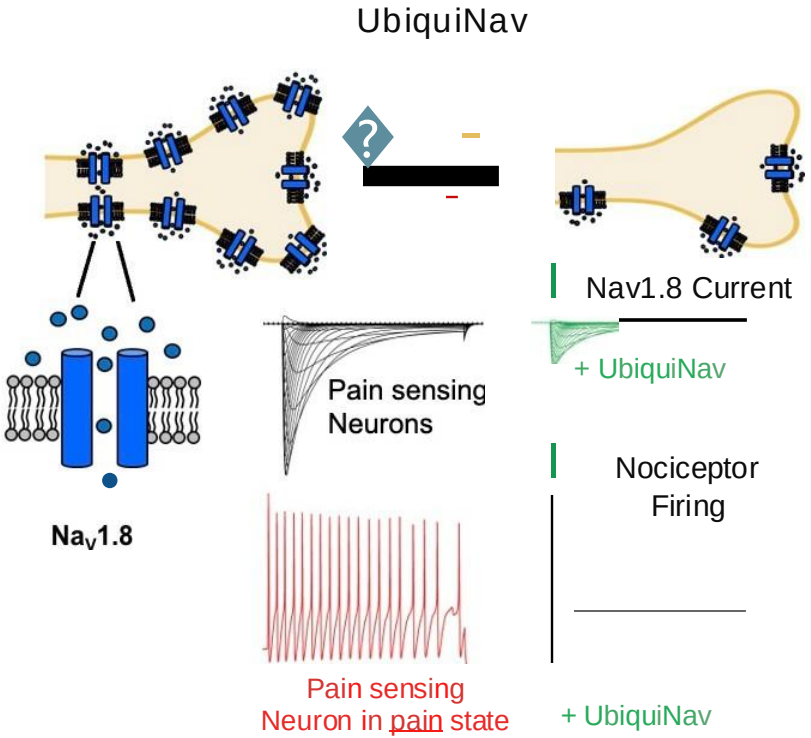
YV 8723: UbiquiNav targets the voltage-gated sodium channel Nav1.8 for degradation

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. Provisioneil 63/580,094. Filed S@pt@mb@r 1, 2023.



CONTACT: Jh9@bQA Kadiri, MD, PhD
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Therapeutics:

Cardiac, Pulmonary, Hepatic, Metabolic and Fibrotic Disease

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

Principal Investigator: Yingqun Huang, MD, PhD

Background:

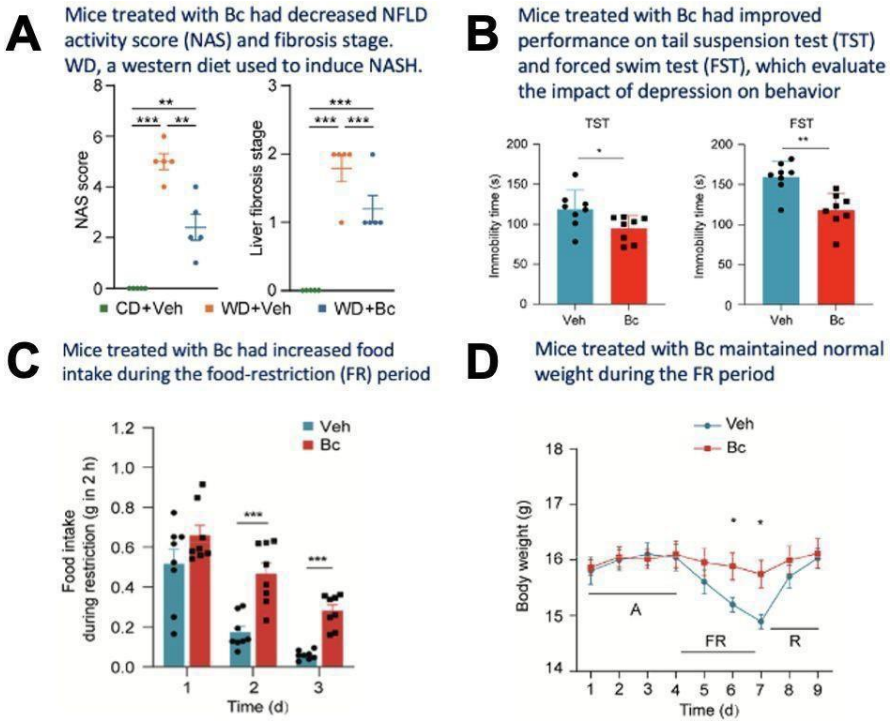
- TET3 knockdown in macrophages ameliorates nonalcoholic steatohepatitis (NASH), liver fibrosis, and endometriosis
- TET3 knockdown in AgRP neurons leads to increased appetite and anti-stress effects (Xie et al, *JCI*, 2022; Lv et al, PNAS, 2023)

Indications: NASH, fibrosis, anorexia, depression, endometriosis

Innovation & Asset: Small-molecule Bobcat339 (Bc) degrades TET3 protein

- Decreases NASH/fibrosis (A) and depressive behaviors (B)
- Improves appetite (C) and body weight (D) in an activity-based mouse anorexia model
- No toxicity, well-tolerated

IP: Patent application pending



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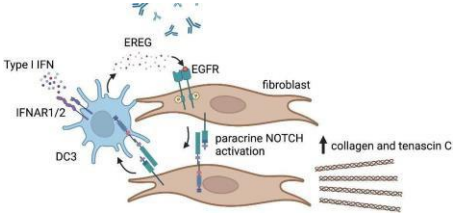
YV8349: Epiregulin Inhibition to Treat Skin and Lung Fibrosis

Principal Investigator: Ian Odell, MD, PhD & Richard Flavell, PhD

Background: EGFR is activated by epiregulin (Ereg)

- Stimulates pro-fibrotic, positive feedback loop between DC3 dendritic cells and fibroblasts

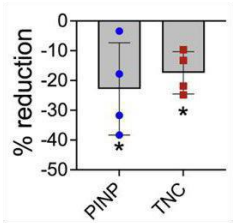


Innovation & Asset: Monoclonal human epiregulin-neutralizing antibody (Ereg Ab)

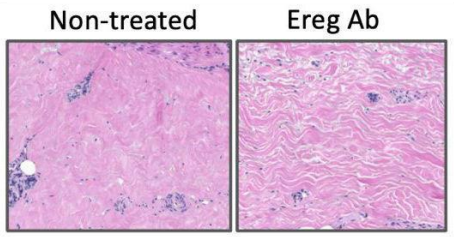
- Ex vivo skin biopsies of patients with systemic sclerosis (**A**, **B**) and Graft vs Host Disease (**C**, **D**) demonstrate decreased pro-fibrotic protein expression and decreased fibrosis on histology
- Ex vivo lung biopsies of patients with idiopathic pulmonary fibrosis demonstrate decreased pro-fibrotic protein expression (dns)
- Increased precision over EGFR and cytokine-targeting therapies
- Full publication in Science Immunology

IP: Patent application pending

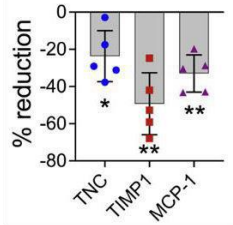
A In skin from patients with systemic sclerosis, Ereg Ab treatment reduces levels of fibrosis markers Pro-COL1A1 N-terminal peptide (PINP) & Tenascin C (TNC)



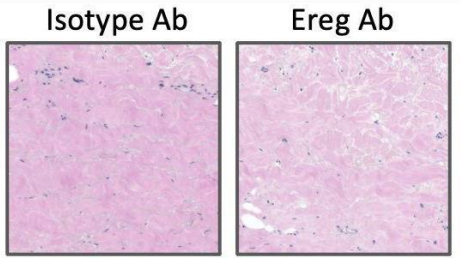
B In human scleroderma skin, Ereg Ab treatment reduces levels of fibrosis (note decreased density of pink fibers with treatment)



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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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

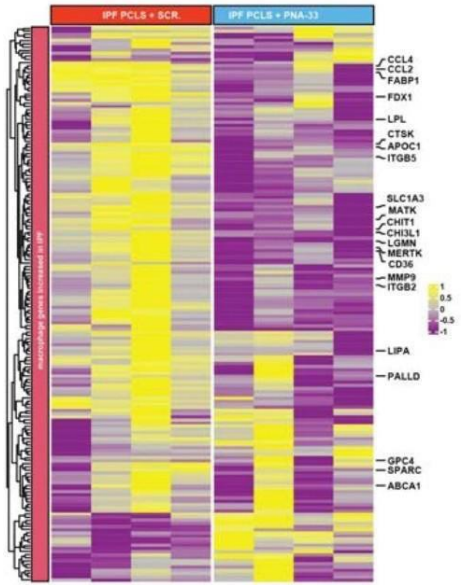
Indications: Idiopathic Pulmonary Fibrosis (IPF)

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

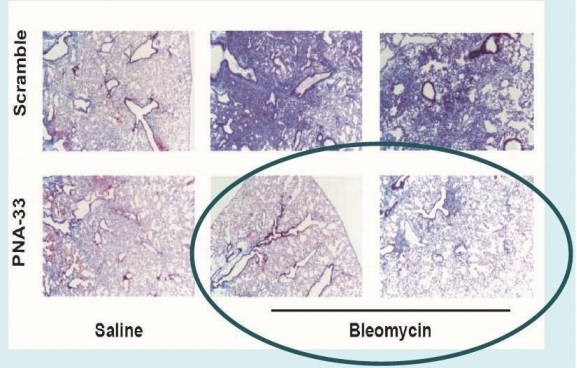
- Decreases lung fibrosis in vivo (mouse models) and ex vivo (samples from mouse and human)
- Improves lung fibrosis on histology in mouse models
- Stable, safe, easily-modifiable compound

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.



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YV7593: Oral 100nM MIF Agonist

Principal Investigator: Lee, Bucala

In Vivo Agonist Intervention in Established Disease

Validity of Therapeutic Hypothesis:

- **Human:** Smokers have decreased circulating MIF **(A)**
- **Patient Selection:** Genotypic (MIF CATT allele) & serum MIF; low
- MIF expression is more common in COPD patients
- **Mouse:** MIF-deficiency results in spontaneous COPD

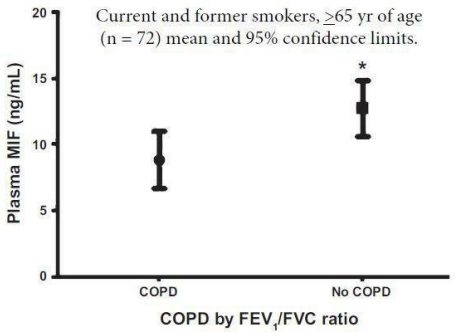
Demonstrated Efficacy:

- **Mouse:** Over-expression of MIF prevents spontaneous COPD
- **Mouse:** Established smoke-induced COPD is treated by daily oral administration of MIF-20 **(C)**: 3 months

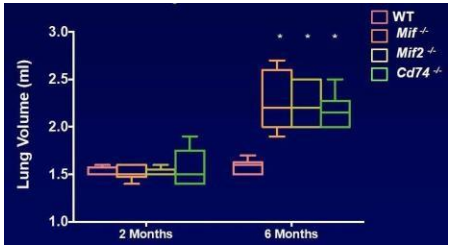
Chemistry: Multiple MIF agonist compositions of matter; enhanced MIF to CD74 binding

Issued

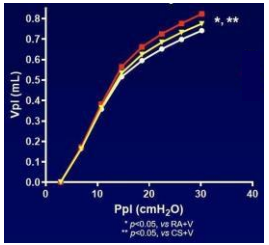
A.

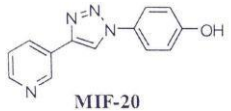


B.



C.





MIF-20
5.2 mg
Chemical Formula: $C_{13}H_{10}N_4O$
Exact Mass: 238.09
Molecular Weight: 238.24

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YV7575: Preservation of TUG-C/Metabolic Disease

Principal Investigators: Jonathan Bogan

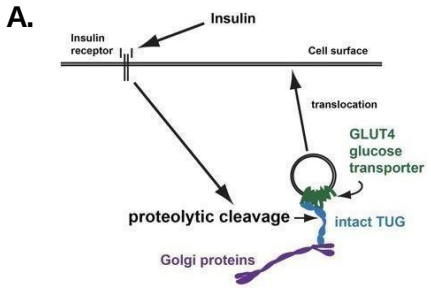
A novel enzymatic target for metabolic disease/obesity

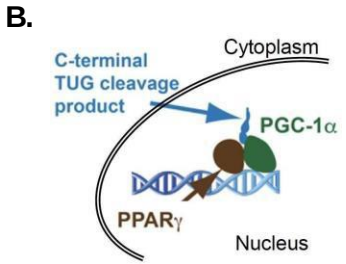
Fundamental Insulin/GLUT4 Biology:
Insulin stimulates the proteolytic cleavage of **TUG** to translocate GLUT4 transporters and to promote glucose uptake **(A). TUG-C**, the C-terminal cleavage product of TUG, translocates into the nucleus **(B),** and modulates metabolic activity via interaction with PPARg and PGC-1a.

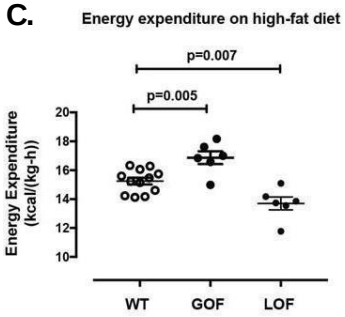
Validity of Clinical Hypothesis:
Human: SNP in PPARg modulates TUG-C binding/PPARg activity

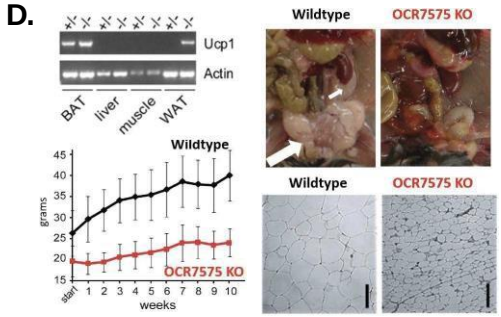
In vivo Validation:

- **Mouse:** TUG-C regulates energy expenditure. GOF = "TUG-C Preservation" increased energy expenditure **(C).**
- **Mouse:** In vivo validation of YV7575 as a target **(D).**









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YV7557: MicroRNA-based Therapeutic for NASH and NAFLD

Principal Investigator: Hyung J. Chun, MD, FAHA

Background: NAFLD is associated with metabolic and cardiovascular disease, insulin resistance, dyslipidemia.

MiR-TA1 promotes vascular inflammation, insulin resistance, obesity and fatty liver.

- miR-TA1-Apoe-/- mice are protected against atherosclerosis in mice.
- MiR-TA1 knockout mice are protected against fatty liver (Figure 1).
- We have developed a novel miR-TA1 inhibitor that protects against atherosclerosis and steatosis in the mice.
- The miR-TA1 inhibitor prevents accumulation of fat in arteries and in the liver.

Treatment: In vivo inhibition of miR-TA1 using subcutaneously delivered antagomiR (direct microRNA complementary inhibitor) results in complete rescue of HFD induced NAFLD in mice and normalization of ALT (Figure 2).

IP Status: PRV filed in 2018

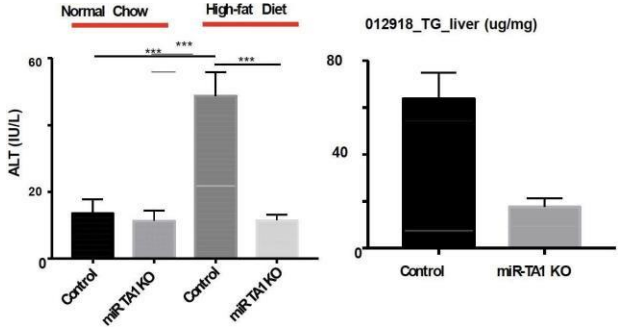

Figure 1. MiR-TA1 KO mice are protected against fatty liver

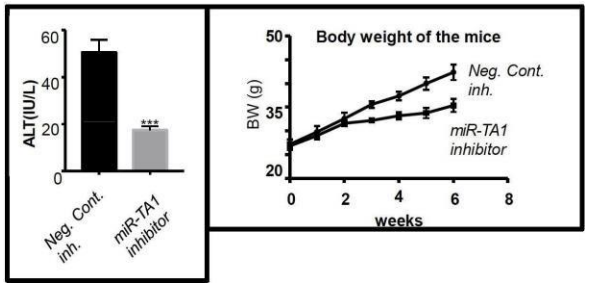

Figure 2. In vivo inhibition of miR-TA1 results in complete rescue of NAFLD in mice and normalization of ALT

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

PARTNERED

Principal Investigator: Michael Simons, M.D.

Background: Syndecans are a distinct family of type-I transmembrane proteoglycan and facilitate growth factor signaling, including that fibroblast growth factors (FGFs) and vascular endothelial growth factors (VEGFs) in endothelial cells.

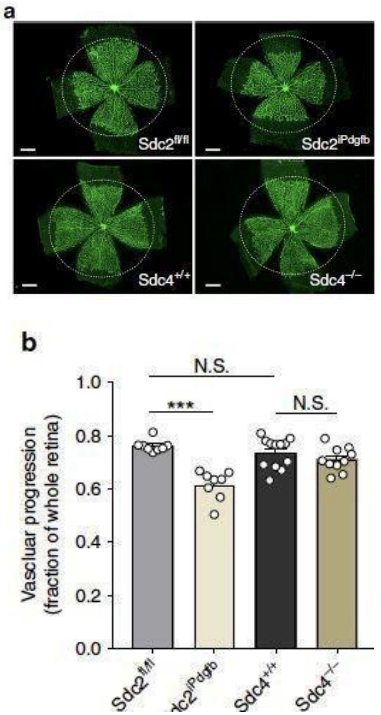
VEFG plays a significant role in regulating vascular permeability in inflammation and tissue injury. The proteoglycan Syndecan-2 (Sdc2) controls VEGFA-induced vascular permeability.

We have shown that Scd2 deletion (global and/or endothelialspecific) result in marked angiogenic and arteriogenic defects and impaired VEGFA165 signaling. We traced this to a core protein sequence of 59 a.a. in the N-terminal domain of Scd2.

Administering a syndecan-2 disrupting agent may be used to treat cardiovascular, neurologic diseases and retinopathy.

References: Corti et al, Nature Comm 2019

IP status: PRV application filed



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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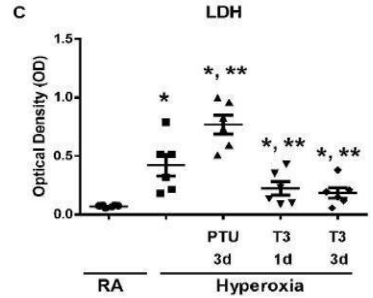
YV7357: Methods of Treating or Preventing Acute Respiratory Distress Syndrome

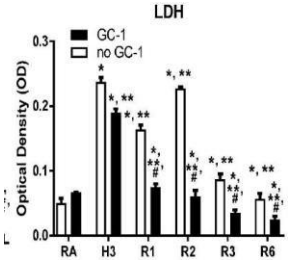
PARTNERED

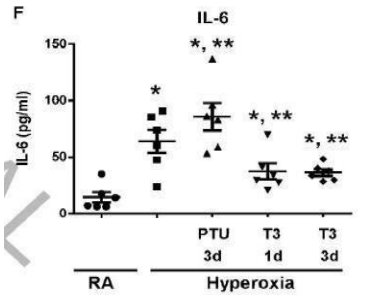
Principal Investigators: Naftali Kaminski, MD; Patty Lee, MD

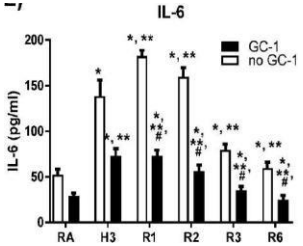
Inhaled Sobetirome as a novel therapeutic agent in ARDS

- 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

YV7314: Novel Clinical Stage NASH Therapeutic

Principal Investigator: Wajahat Mehal, DPhil, MD

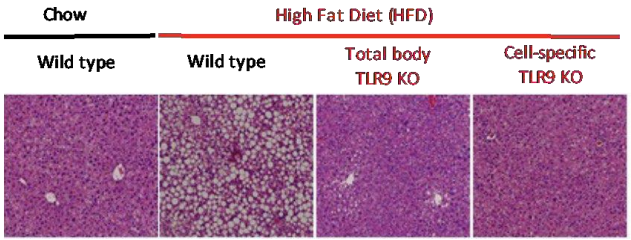
Non-Alcoholic Steatohepatitis (NASH) is a form of sterile inflammation that is driven by obesity, metabolic syndrome and type 2 diabetes. It can progress to fibrosis, cirrhosis, and liver cancer. There are no approved therapies. By 2020, NASH will be the leading cause for liver transplants.

About YV7314:

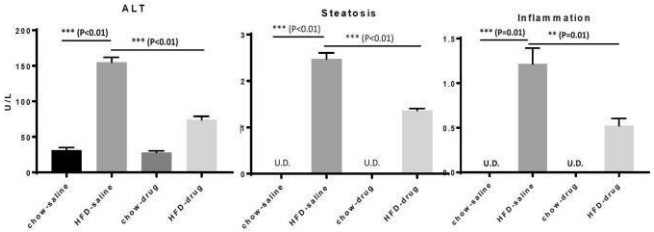
- A novel oligonucleotide antagonist of TLR7/9.
- Excellent Phase 1 safety and tolerability data; Phase 2 safety data.
- Strong in vitro and in vivo efficacy in the HFD mouse models of NASH.
- Unique mechanism of action: targets inflammation and oxidative stress pathways that lead to liver fibrosis, while majority of current NASH drug candidates (18 out of 27 active NASH programs) target metabolic component of the disease.
- Biopharma-developed drug, in-licensed by Yale for clinical development for new indications, including NASH and liver fibrosis.

IP status: four issued patents and pending applications with COM and MOT claims; pre-IND package for acute indications, Right of Reference, phase 1-2 clinical data from previous clinical trials for different indication (the phase 2 results did not meet endpoints).

1. Mice with total body and Kupffer cell-specific loss of TLR9 are protected from NASH caused by high fat diet (HFD).



2. YV7314 reverses liver injury in the HFD model of NASH.



IP status: 7 issued patents, extending to 2030; Clinical data package and Right of Reference to active IND. Lead Inventor: Wajahat Mehal, M.D., D. Phil.

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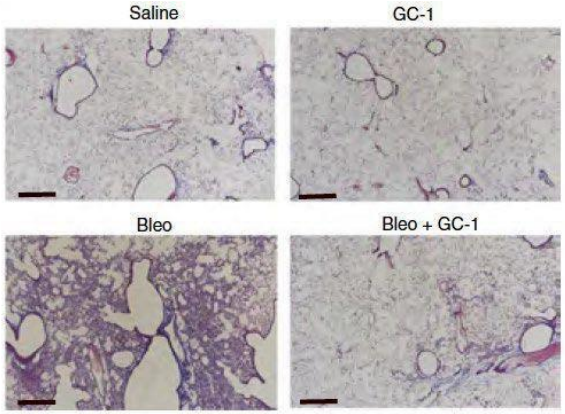
YV7270: Thyromimetics for fibrotic lung diseases

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, Nature Medicine 2018

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YV7100: NASH - Allosteric Targeting of Phosphatase

Principal Investigator: Anton Bennett

Tissue-specific KO's of "Phs1" Phosphatase Prevents NASH

Validity of Therapeutic Hypothesis:

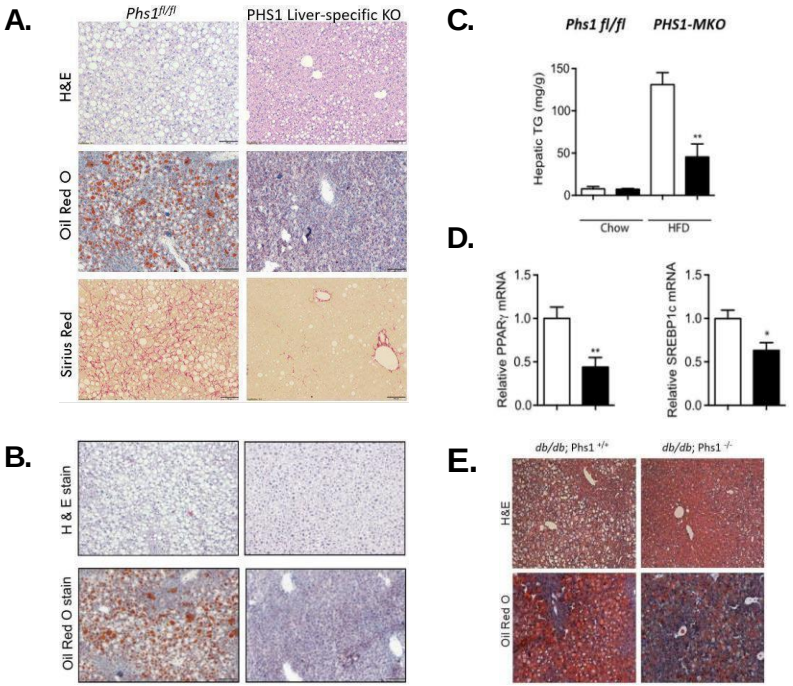
- **Mouse:** global KO protects against high-fat diet ("HFD")-induced NASH
- **Mouse:** liver-specific KO protects against HFD-induced NASH
- **Mouse:** liver-specific KO on CDAA diet - Phs1 required to develop NASH **(a)**
- **Mouse:** liver-specific KO protects against HFD-induced NASH **(b)**, elevated liver triglycerides **(c)**, reduces PPARγ and SERP1c mRNAs **(d)**
- **Mouse:** genetically obese (ob/ob) Phs1 KO are protected against NASH **(e)**

Drugability of Class: Allosteric site identified and successfully targeted for the structurally related Phs-5 Phosphatase.

Commercial: "Phs5" programfor multiple fibrosis indications partnered with a top Pharma.

Faculty Resources:

- Validated primary and secondary screens established
- Library of Phs family allosteric scaffolds available for medicinal chemistry
- Cell lines, mouse models, assays, commercial experience **IP/Assets:** diverse expertise, models, crystal structures, published biology and pathw ay understanding, proven team



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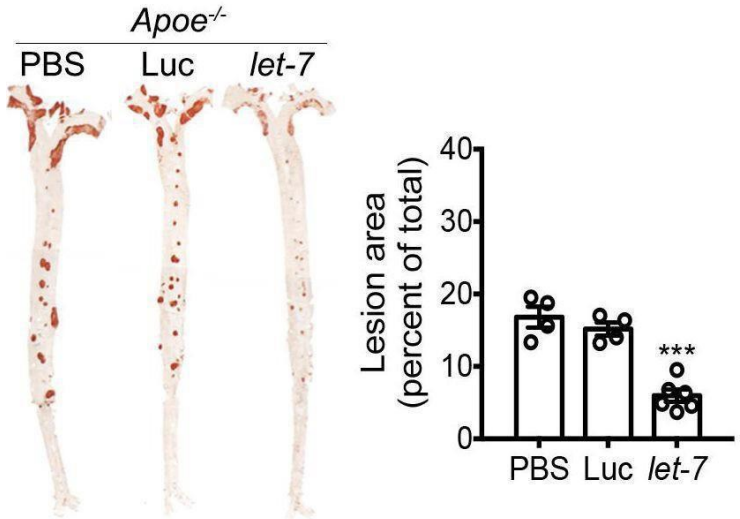
YV6925:Molecular Therapies of Atherosclerosis

PARTNERED

Principal Investigator: Michael Simons, M.D.

Endothelium-specific delivery of let-7 miR for treating Atherosclerosis

- Atherosclerosis is responsible for the vast majority of cardiovascular disease. Currently available therapy (statins) slow down, but do not reduce the disease.
- Suppression of TGF, FGF and let-7 miRNA signaling in the endothelium can be used to reduce the size of atherosclerotic plaque and decrease overall atherosclerosis burden.
- A genetic proof of this concept has been obtained in mice using endothelial-specific TGFR1/R2 knockout.
- Additional supporting data available from human samples
- **Indications:** atherosclerosis, CAD/MI/angina, stroke, peripheral vascular disease
- **References:** Nat Metab 2019 Sep;1(9):912-926
- **IP status:** US 16/086,809



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

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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

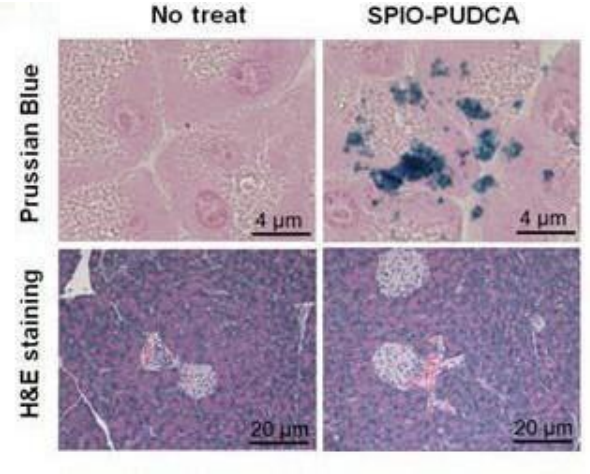

FIG. Histology images of pancreatic sections from mice that were orally treated with PBS or PUDCA nanoparticles containing iron oxide (SPIO-PUDCA). Iron Oxide is assayed using the Prussian Blue stain which appears distinct in the pancreas.

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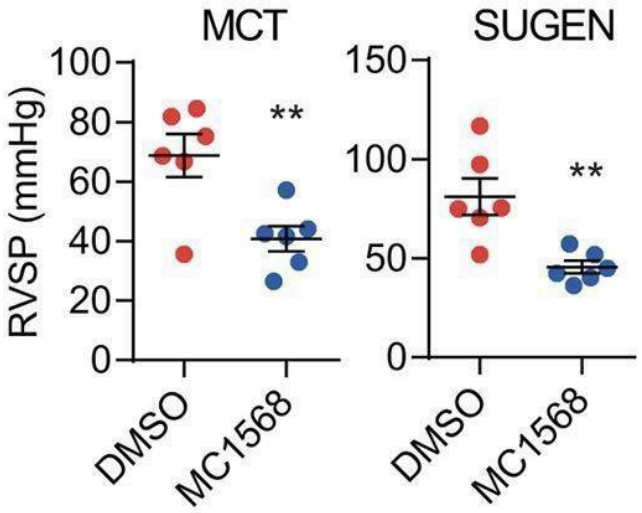
YV6370: Therapeutic for Pulmonary Arterial Hypertension

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.
- **Filed and Issued Patents:** 9340787; 20140155459



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).

Yale

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YV6368: Thyroid hormone for Fibrotic Lung Diseases

PARTNERED

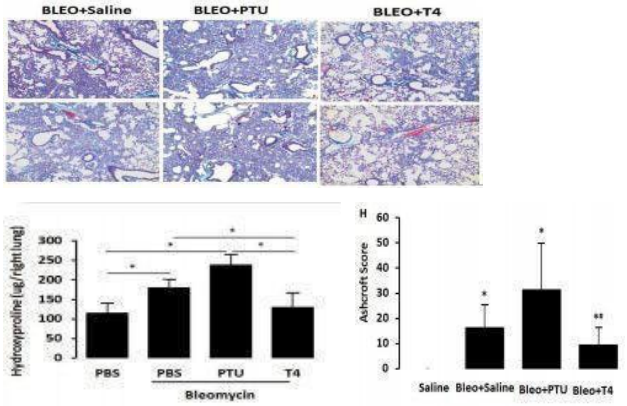
Principal Investigator: Naftali Kaminski, M.D.

Thyroid hormone as a novel therapeutic agent in fibrotic lung diseases

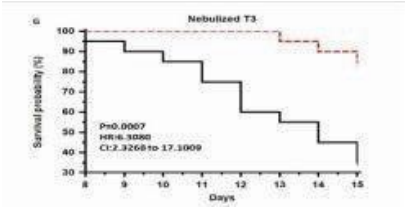
- Idiopathic pulmonary fibrosis (IPF) is a lethal fibrotic lung disorder. The median survival of patients with IPF is 3.5-4

  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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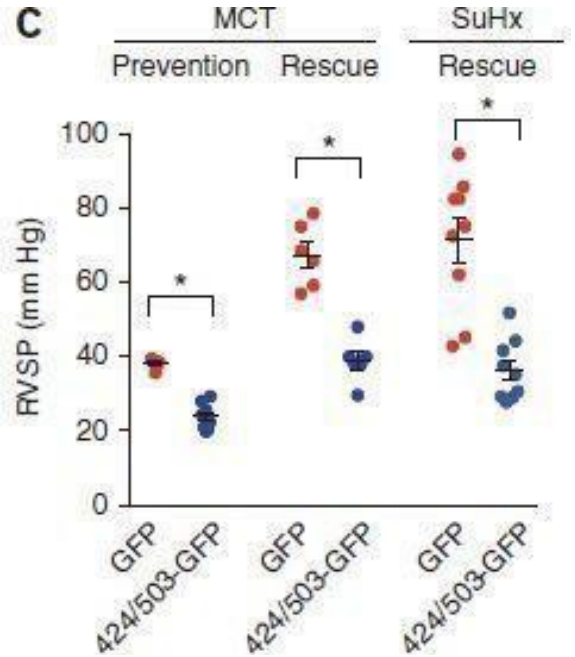
YV5799: Novel Therapeutic for Pulmonary Arterial Hypertension

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:** US20140155459 A1



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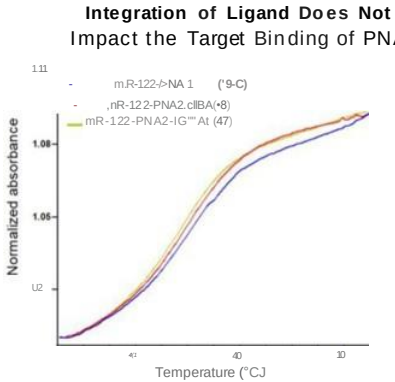
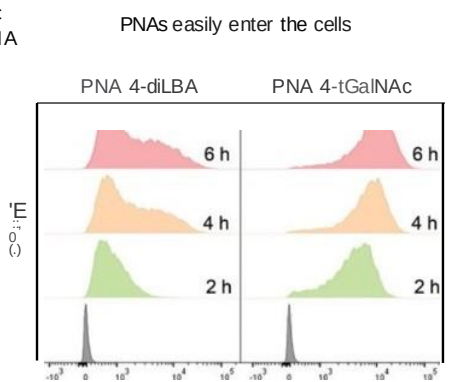
YALE VENTURES

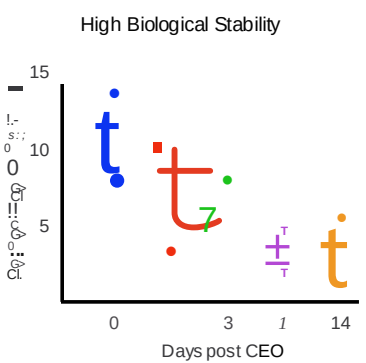
YV 8151: Synthetic microRNA-33 Inhibitors to treat IPF

- **Problem:** IPF affects 190,000 patients in the US and ~6M WW, with 30,000 - 40,000 new cases each year. Half of the patients will die 3 years after diagnosis (30,000 deaths a year). Lung transplantation remains the only curative option. Two FDA approved drugs have been on the market since 2014 with sales> $1.98, but neither cure IPF nor improve patients' quality of life. The market is expected to reach $4.28 by 2025.
- **Background:** Metabolically disturbed profibrotic macrophages dominate IPF lungs; miR-33 is increased in IPF lung macrophages; the Tg mice with targeted miR-33 KO are protected against bleomycin-induced lung fibrosis.

- **Innovation:** We designed and tested PNA-33 and showed in in-vivo & ex-vivo models of IPF that it reduces lung fibrosis, expression of many fibrotic genes and secretion of collagen.
- We are working on topical lung delivery of PNA-33 ((intranasal or inhalation).
- **Principal Investigator:** Farida Ahangari, Ph.D.
- **IP Status:** 63/188,759, filed 5/14/2021







Wang Y et al, Science Advances, 2023, Kumar V et al, Advanced Healthcare Material, 2023

Therapeutics:

Inflammatory and
Autoimmune disorders,
Immunomodulation

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.

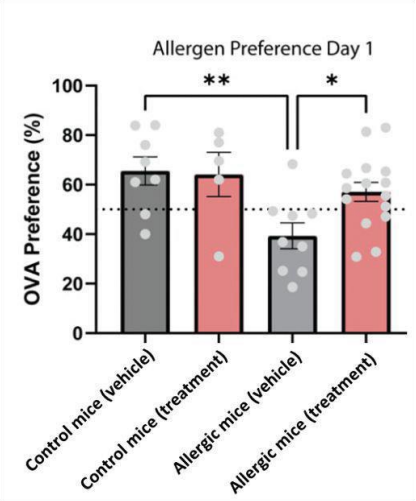
Indications: Suppression of food allergic reactions

Innovation & Asset: Dr. Ruslan Medzhitov's team uncovered a novel method of treating food allergy with a known, orally-active, small molecule inhibitor of a key inflammatory enzyme

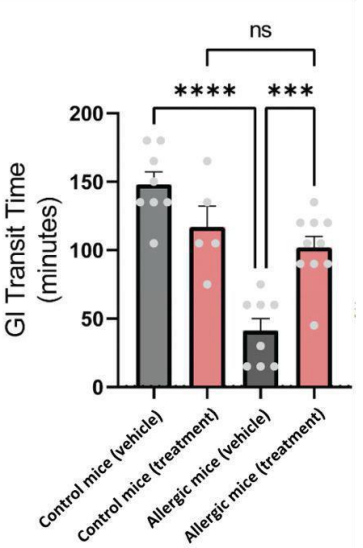
- In vivo mouse data demonstrates the molecule:
  - Reduces avoidance of allergen (**A**) and ameliorates allergen-induced diarrhea (**B**)
  - Normalizes temperature drop, mast cell hyperplasia, gross intestinal pathology (dns)
- Advantages of this method over antibody pre-treatment such as omalizumab include no risk of serum sickness, no injection needed, cheaper

IP: Patent application pending

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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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**

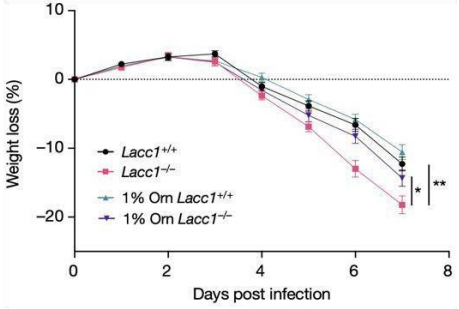
Indications: Bacterial infections, Inflammatory conditions

Innovation & Asset: Rescuing LACC1 deficiency with L-Ornithine

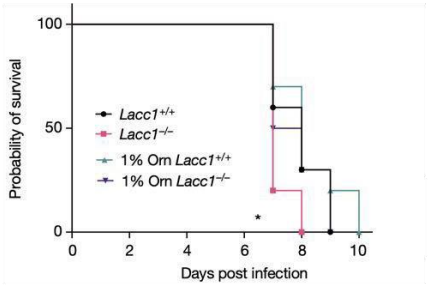
- **Decreases pro-inflammatory cytokine release from macrophages (in vitro, dns)**
- **Mitigates weight loss (A), improves survival (B), and decreases bacterial burden (C) in LACC1-KO mice**
- **Simple and economical production**

IP: Unpublished Patent Application

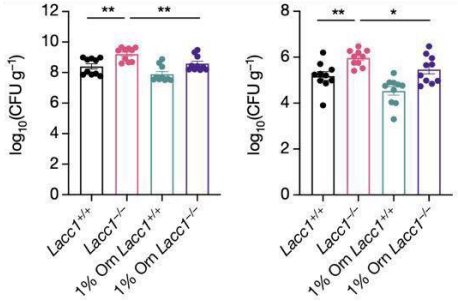
A L-Ornithine supplementation rescues weight in LACC1-KO mice after S. Typhimurium infection.



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.



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YALE VENTURES

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

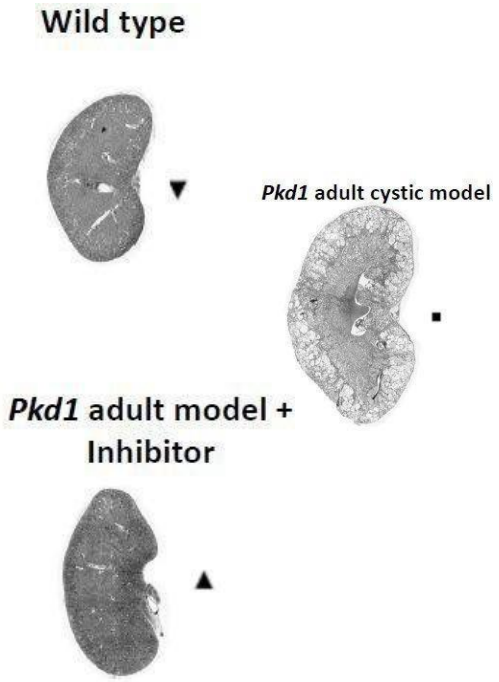
Principal Investigators: Stefan Somlo, MD, Sorin Fedeles, PhD, MBA

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



IP status: PCT/US22/72926

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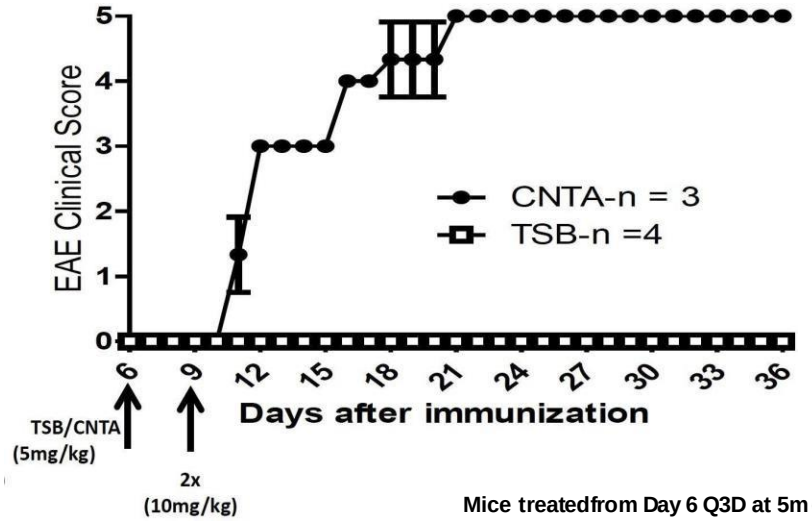
YALE VENTURES

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 5mg/kg i.p. except for a 10mg/kg dose on Day 9.

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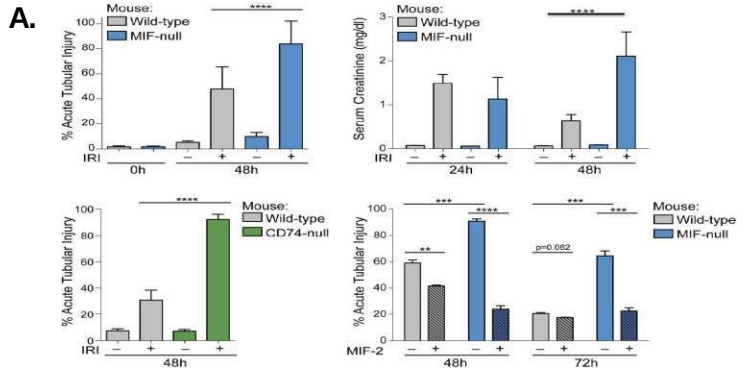
YV5557: MIF-2 for Acute Kidney Injury (AKI)

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:** Issued & Pending Patents



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

Yale

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YALE VENTURES

YV8731: HIF Inhibition for the Treatment of Cutaneous Lupus

Principal Investigator: Alicia Little, MD, PhD

Background:

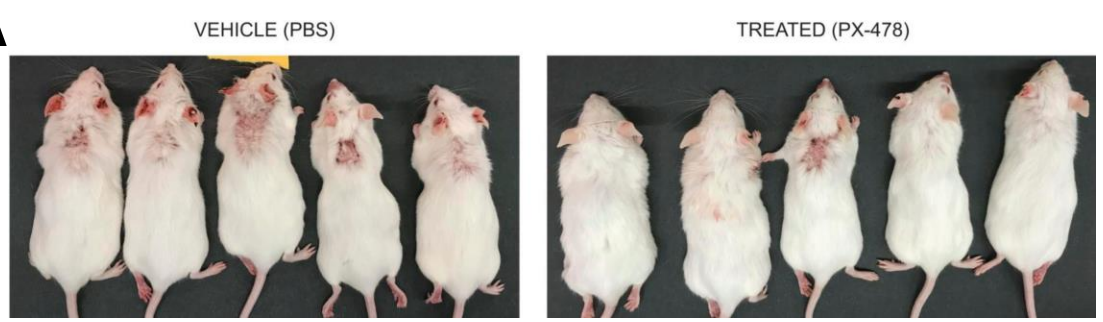
- Hypoxia-inducible factor-1 (HIF-1) upregulation is responsible for the inflammatory T-cell phenotype in lupus nephritis (Chen et al, *Sci Trans Med*, 2020), but its role in cutaneous disease was previously undefined

Indications: Cutaneous lupus erythematosus (CLE)

Innovation & Asset: Novel, druggable pathway implicated in cutaneous lupus erythematosus:

- Murine models of cutaneous and systemic lupus erythematosus demonstrate reduced clinical skin disease with pharmacological HIF-1a inhibition (A)
- Human discoid lupus erythematosus patients display a similar molecular profile to murine models, suggesting susceptibility to HIF-1a targeting (B)

IP: Patent Application Pending



(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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YV8415: Novel peptide to promote neovascularization in critical limb ischemia

Principal Investigator: Mehran M. Sadeghi, MD

Background:

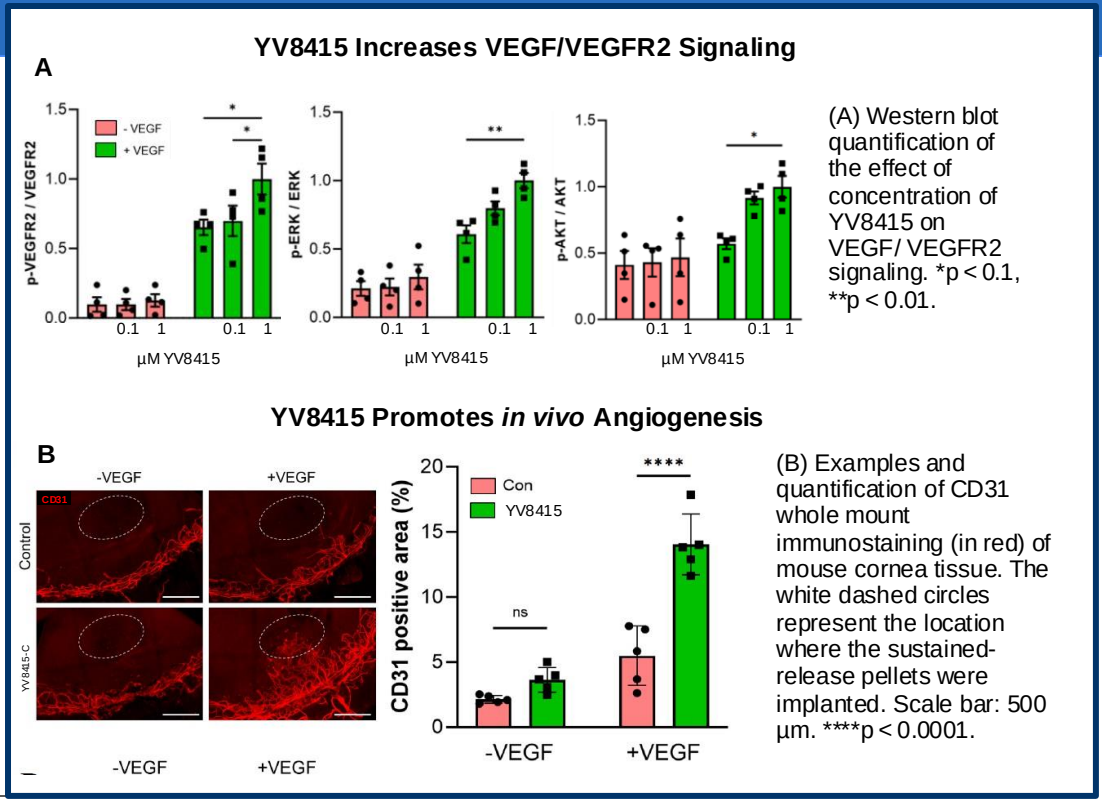
- 2.5M people in the U.S. have CLI, the end stage of peripheral artery disease
- CLI has a 50-60% 5-year mortality and is estimated to contribute ~$4B in annual U.S. health care costs

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: Provisional Patent Filed



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

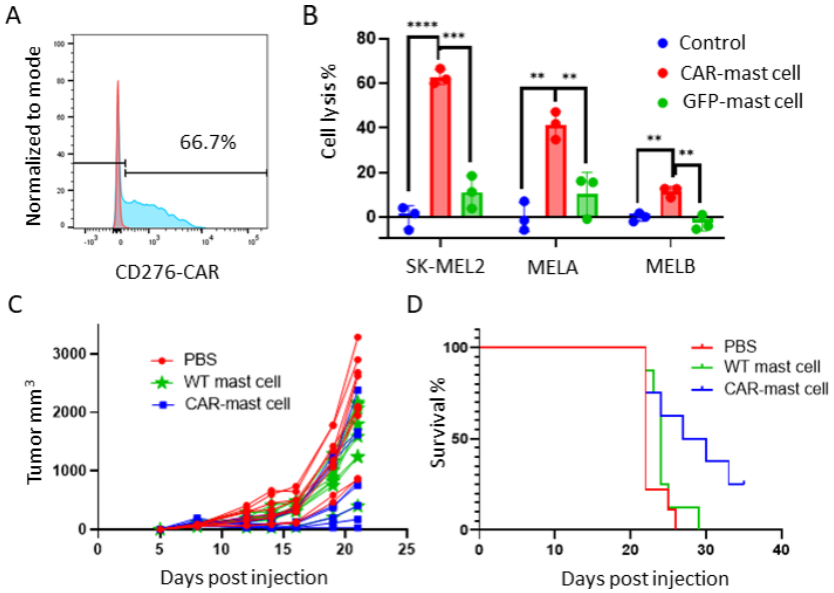


Fig.1 Cytotoxicity of anti-CD276 (B7H3) CAR-mast cells. A) Expression of CD276 CAR in mast cells. **B)** CAR-mast cells were incubated with CD276+ human melanoma cells at an E:T = 5:1. **C)** Monitoring tumor growth in C57BL/6 mice xenografted with MC38-CD276+ cells. Each mouse received 5x10^6 MC38 cells 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

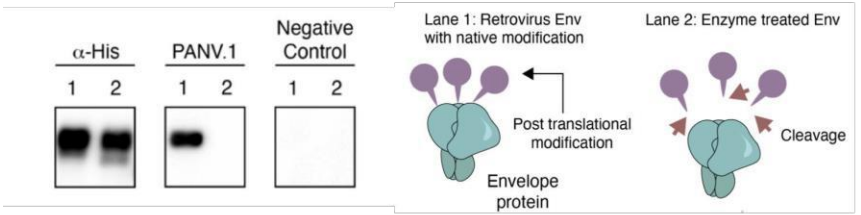
Vaccines & Infectious Disease

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

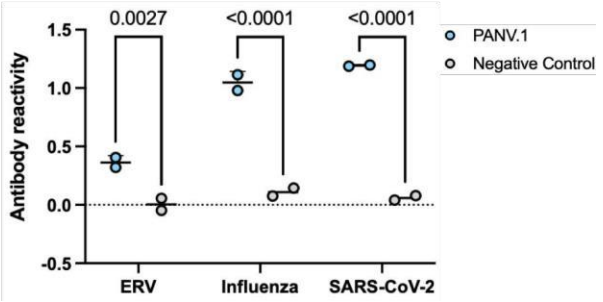
Principal Investigator: Akiko Iwasaki, PhD

- **Background:** Viral outbreakspresent a significant global health challenge
  - 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 multiple virus 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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YV8038: 20 nM SARS-CoV-2 Protease Inhibitors

Principal Investigator: William Jorgensen

Structure-based design of Mpro Antagonists

- A potent (20 nM) series of small molecule, 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 & commerciallyviable synthetic routes

Figure 1

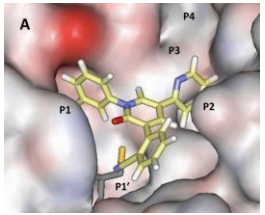


Figure 2

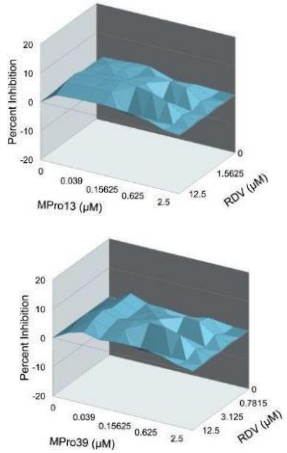


Table 1

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		

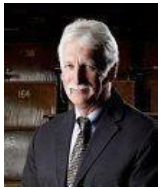
[a] Fluorescence of compound interfered with assay.

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
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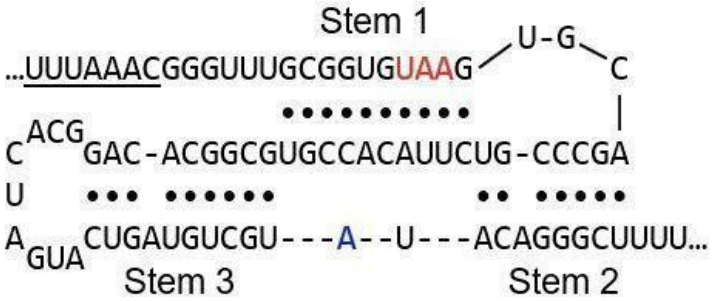
YALE VENTURES

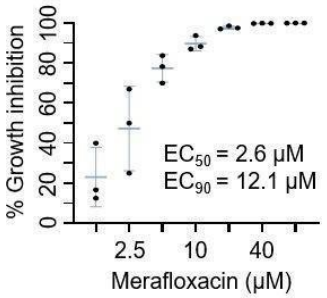
YV7981: Compounds and Compositions for Disrupting Programmed Ribosomal Frameshifting

Principal Investigator: Junjie Guo

- Programmed ribosomal frameshifting is a prevalent and critical feature among RNA viruses
- Dr. Junjie Guo's lab at Yale has developed a platform to rapidly identify chemical modifiers of ribosomal frameshifting and has identified compounds that either enhance or suppress ribosomal frameshifting of SARS-CoV-2 and other beta coronaviruses.
- Frameshift inhibition significantly inhibited SARS-CoV-2 replication in Vero E6 cells.
- **Intellectual Property:** Patent application pending.
- **Reference:** Sun et al., bioRxiv (2020) https://doi.org/10.1101/2020.10.21.349225



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).



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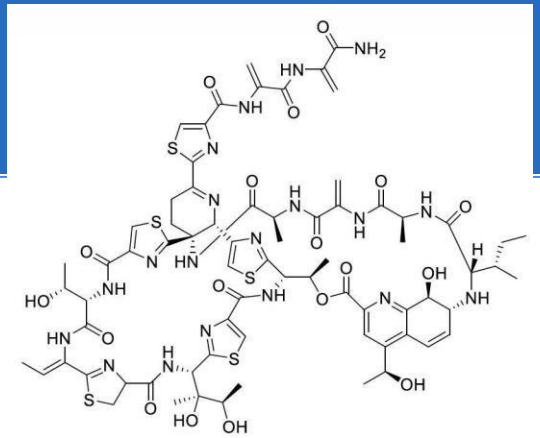
YALE VENTURES

YV7705: Novel Thiostrepton analogs with Improved solubility



Principal Investigator: Jon Ellman

- Thiostrepton (shown to the right) is a natural product with potent activity against Gram positive bacteria, including MRSA. Clinical use of Thiostrepton in humans however is precluded by the compound's poor aqueous solubility.
- Using a novel chemistry approach, a series of semi-synthetic analogs has been generated. Evaluation of these analogs demonstrates that increased solubility can be achieved while retaining antibacterial activity (table to right).
- Additional analogs are under evaluation with the aim of optimizing solubility and potency for clinical utility of this compound class.

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

- **Intellectual Property:** Patent application pending.
- **Reference:** Cobalt (III)-Catalyzed C-H Amidation of Dehydroalanine for the Site-Selective Structural Diversification of Thiostrepton.
- R.J. Scamp, E. deRamon, E.K. Paulson, S.J. Miller & J.A. Ellman. Angew. Chem. Int. Ed. 59: 890 (2020)
- https://onlinelibrary.wiley.com/doi/10.1002/anie.201913886

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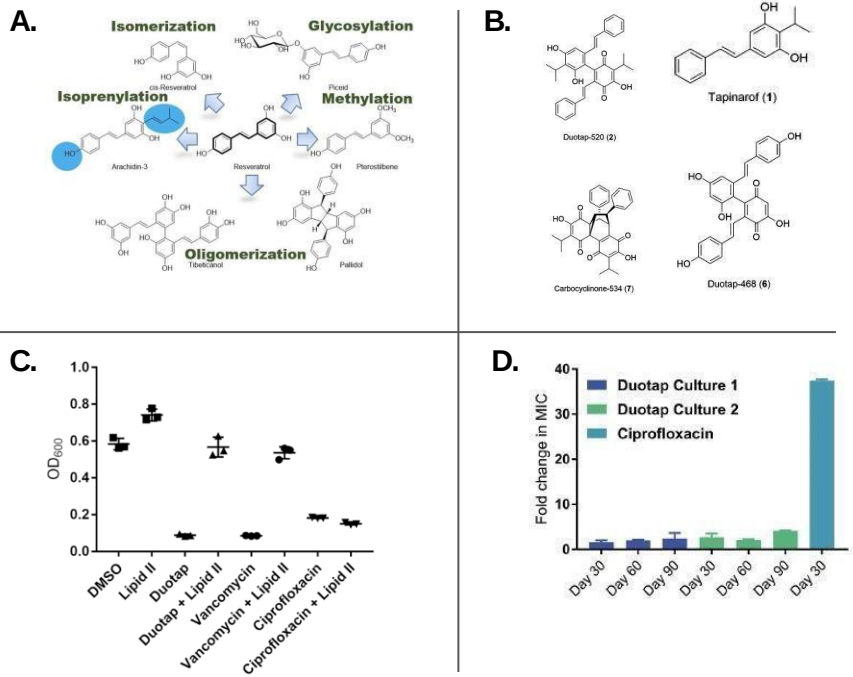
YV7643: Novel Stilbenes for immuno-dermatology and antibiotics (MRSA/VRE)

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).
- Intellectual Property



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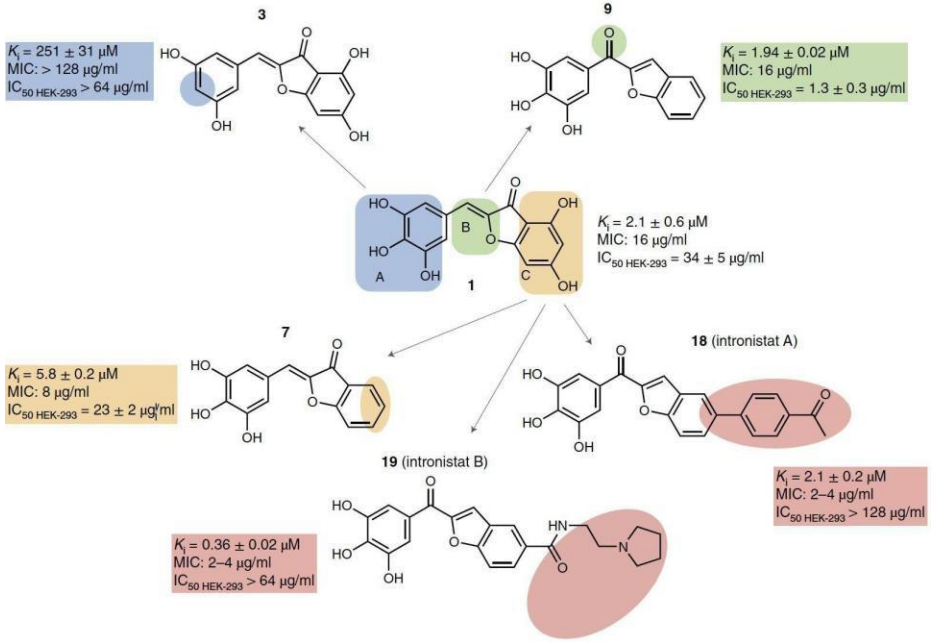
YV7345: Novel Small-molecule Antifungal Agents

Principal Investigator: Anna Pyle

- Group II Introns are found in fungi but not in mammals.
- A high-throughput screen for inhibitors of identified 16 reproducible hits of Group II intron splicing
- Most potent inhibitor has MIC of 2 µg/ml vs Candida parapsilosis (comparable with Amphotericin B)
- Non toxic in mammalian cell culture model



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

Principal Investigator: Ellen Foxman

- Developed a quick and accurate diagnostic test to distinguish viral and bacterial respiratory infections from patients' nasopharyngeal swabs.
- This method detects hosts' responses to infections instead of testing each specific virus.
- This is a non-blood based point of care diagnostic test to be used at any medical provider's office.
- Patent Applications Pending

A

		Virus	
		Positive	Negative
Test	Positive	21	0
	Negative	2	45

		95% CI
Sensitivity	0.91	0.72-0.99
Specificity	1.00	0.92-1.0
PPV	1.00	0.84-1.0
NPV	0.96	0.86-1.0
Accuracy	0.97	0.90-1.0
Prevalence	0.34	

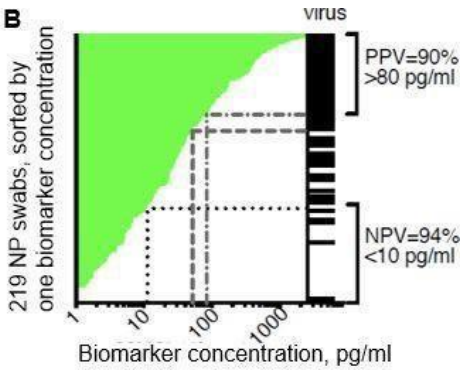

Figure 1: A. Test performance of mRNA biomarker signature. B. Possible rule in/rule out test for viral respiratory infection based on one biomarker protein level, using data from 219 nasopharyngeal swabs.

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YV7021: Protection from Autoimmune Disease

Principal Investigator: Martin Kriegel

Treating Autoimmune Diseases by Preventing Translocation of the Autoimmune-Promoting Pathobiont

- 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.
- Intellectual Property: Patent issued on July 13, 2021 (U.S. Patent No. 11,058,756)

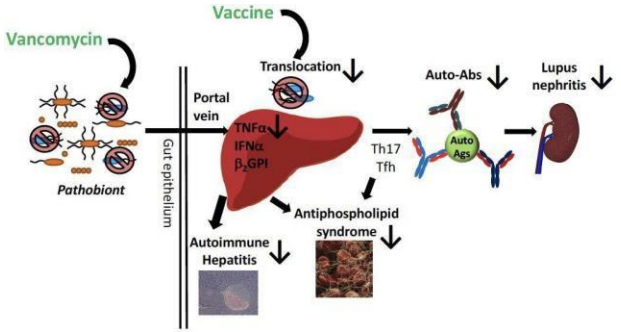

Figure 1. Schematic illustration of the mechanism of action of a gut pathobiont on autoimmunity, and how the antibiotic vancomycin or a vaccine against the pathobiont protect from autoimmune diseases by preventing translocation of the autoimmune-promoting pathobiont.

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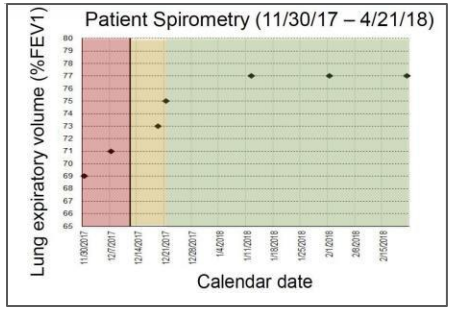
YV6978: Phage Therapy for Restoring Antibiotic Sensitivity to Bacterial Pathogens

PARTNERED

Principal Investigator: Paul Turner, Ph.D.

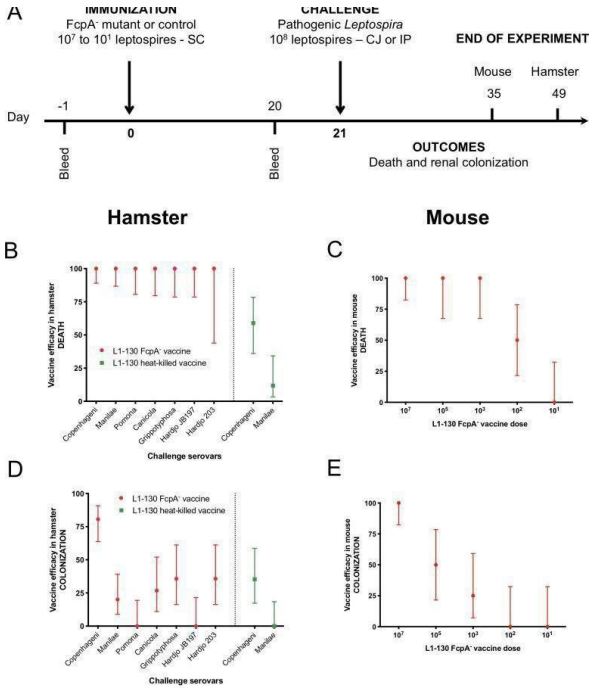
- P. aeruginosa causes infections that are notoriously difficult to manage due to low permeability of the outer membrane and antibiotic multi-drug efflux (Mex) system.
- OMKO1 is a phage that utilizes OprM/Mex as a receptor-binding site.
- Bacteriophage-induced selective pressure can reverse antibiotic resistance in multidrug resistant P. *aeruginosa.*
- **This phage has been used successfully to treat infections in more than 10 patients** via compassionate use exemption.
- **Reference:** Chan *et al.* (2016) Sci Rep
- **IP status:** pending applications US16/095,041 and EP17790237.6



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

YV6291: Potent Anti-Virulence Factor Against MRSA

Principal Investigator: Erol Fikrig, MD

The Ixodes scapularis tick antifreeze glycoprotein, IAFGP, functions as an antivirulence agent against diverse bacteria, including methicillin-resistant Staphylococcus aureus.

Recombinant IAFGP and a peptide, P1, derived from this protein bind to microbes and alter biofllm formation.

Transgenic lafgp-expressing flies and mice challenged with bacteria, as well as wild-type animals administered P1, were resistant to infection, septic shock, or biofllm development on implanted catheter tubing.

Antifreeze protein facilitates host control of bacterial infections and suggest therapeutic strategies for countering pathogens

rIAFGP and P1 can be used as potent antimicrobial agents, alone or in combination with other antibiotics such as Ciprofloxacin and Daptomycin, and against antibiotic-resistant bacterial infections.

- **IP status:** US10,092,626B2, issued 10/9/2018
- **Reference:** Heisig, Martin *et al.* (2014) Cell Report

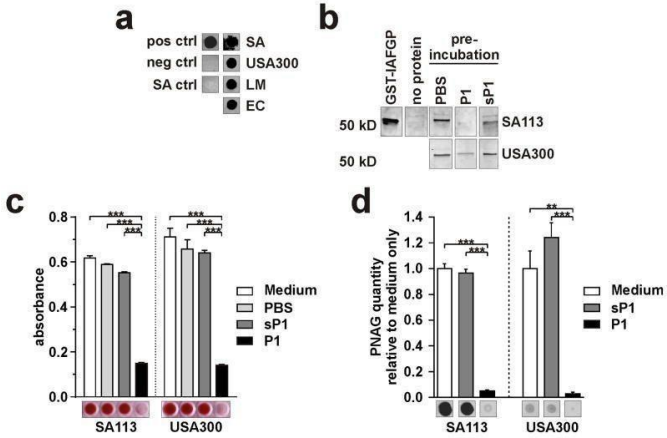
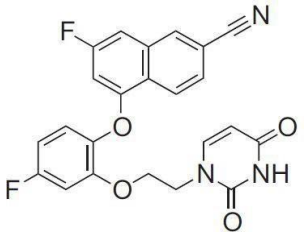


Figure: Binding of P1 to Staphylococcus aureus interferes with biofilm formation in vitro. A: S. aureus SA113, the methicillin-resistant USA300 JE2 isolate, L. monocytogenes EGDe and E. coli DH5α were incubated with biotinylated P1 (pos ctrl)in DMSO

YV6245: In vivo Long-term CR NNRTI

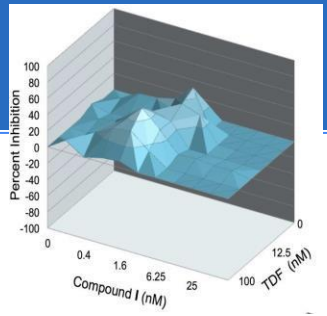
Principal Investigators: William Jorgensen, Karen Anderson, Mark Saltzman

- 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)
- Highlysoluble with 2-21 nMpotency vs. drug-resistant strains, including K101P (e.g., rilpivirine ineffective against K101P) in MT-2 T-cell/HIV-1 assay
- Excellent ADME-Toxand 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
- Issued US Patent 9,382,245 and related pending IP & Publication 1 & 2



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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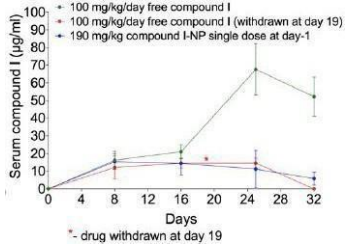

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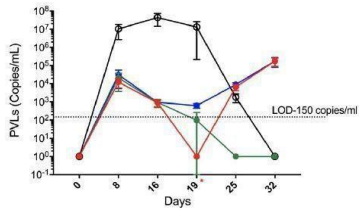

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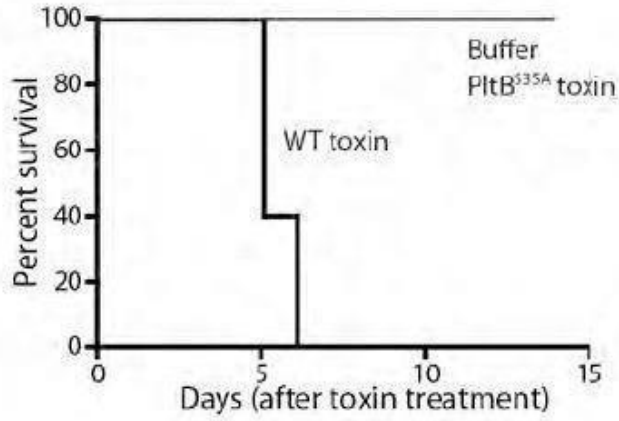
YALE VENTURES

YV6185/6779: Vaccine Candidate for Typhoid Fever

Principal Investigator: Jorge Galan, PhD, DV

- 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 are only about 70-75% effective overall.
- Need for more effective vaccines to prevent the contraction and spread of this disease.
- 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.



- **Reference:** Song et al. (2013) Nature
- **Patent Applications:** PCT/JP2001/000377; WO2002057760A1

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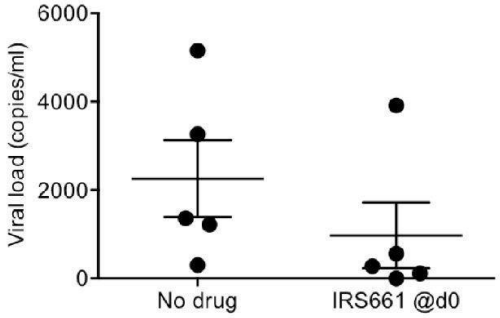
YALE VENTURES

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 TollHike 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

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YV5753: Anti-HIV Agents

Principal Investigator: William Jorgensen

Catechol Diether Analogues as Anti-HIV Agents

- HIV reverse transcriptase (RT) remains a key molecular target 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 with high therapeutic potential with low toxicity leading to a very high therapeutic index.
- Issued US Patent & Reference

YV6109: Catalyst-Dependent Synthesis of Glycopeptide Derivatives

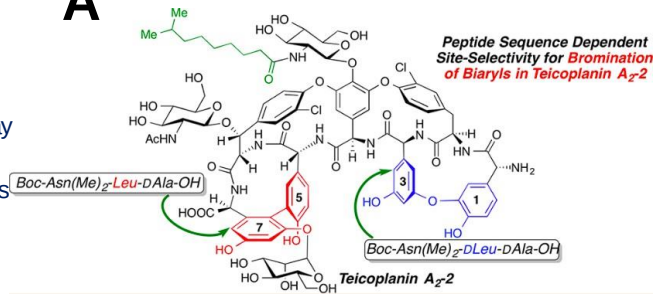
Principal Investigator:

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: Patent: "Site-Selective Functionalization Of Glycopeptide Antibiotics"

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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Cellular Therapy, Regeneration & Wound-healing

YV8255: Sarxion Biologics, Porcine Decellularized Tissue Platform

Principal Investigator: Themis Kyriakides, PhD

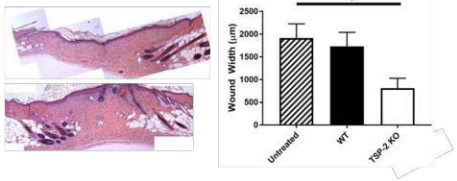
- **Background:** Current tissue grafts/materials have limited efficacy and duration
  - Many common complications (e.g., dislodging) are caused by poor graft-host tissue integration
  - TSP-2 protein modulates extracellular tissue morphology & compatibility (**A**)
- **Indications:** Hernia patches, 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 vascular graft failure (**D**)
  - TSP2 KO pig skin processing and results (**E**)
- **IP:** Multiple Patent Families

A TSP-2 modulation of ECM. Effects of TSP-2 KO.

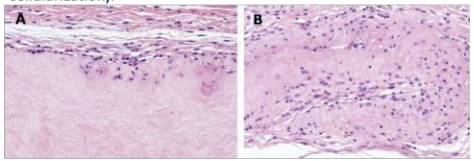
↓ TSP-2 → ↑ ECM remodeling → ↑ Angiogenesis & integration

↓ Thrombus formation

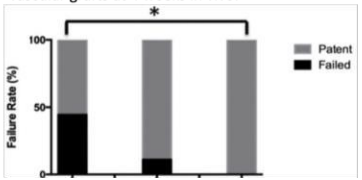
B TSP-2 knockout-derived hydrogel improves wound healing in diabetic mice (day 21 after 6mm wound).
Left (T): Wild-type gel treatment.
Left (B): TSP-2 KO gel treatment.
Right: Significant reduction in wound width.



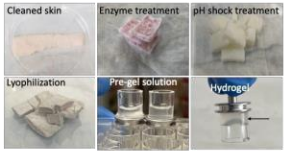
C Mouse skin hydrogel integration in vivo
Left (A): Wild-type skin hydrogel (poor integration and cellularization).
Right (B): TSP-2 KO skin hydrogel (note integration and cellularization).



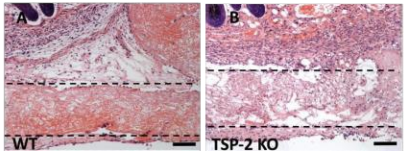
D Failure rate of unmodified (left), WT-ECM modified (middle), and TSP2-KO-ECM modified (right) vascular grafts at 4 weeks in vivo.



E Pig skin step-wise processing to form hydrogel



Pig skin hydrogel integration in vivo
Left: Pig skin hydrogel from WT animals (lack of cells).
Right: Pig skin hydrogel from TSP2 KO animals.



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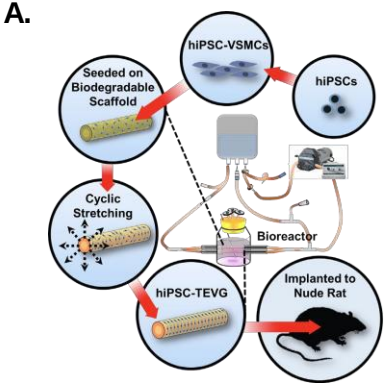
YV7839: Human iPSC-based Tissue Engineered Vascular Graft

PARTNERED

Principal Investigator: Laura Niklason

- Current Tissue engineered vascular grafts (TEVGs) developed from primary cells have limited expandability and donor-donor functional variation of the primary cells.
- Dr. Yibing Qyang's lab has developed a method to generate TEVGs using vascular smooth muscle cells derived from human induced pluripotent stem cells (hiPSC-VSMCs).
- hiPSC-TEVGs have mechanical strength comparable to that of saphenous veins employed clinically as vascular grafts, and maintained mechanical function following rat implantation.
- This method provides non-immunogenic TEVGs
- **Intellectual Property:** Patent application pending
- **Reference:** Cell Stem Cell 26, 1–11, Feb 6, 2020

A.

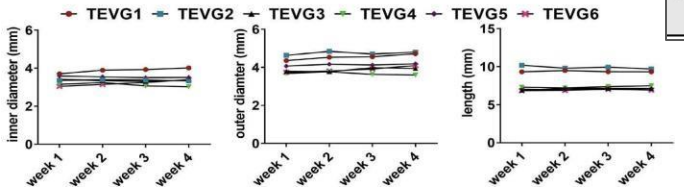


B.

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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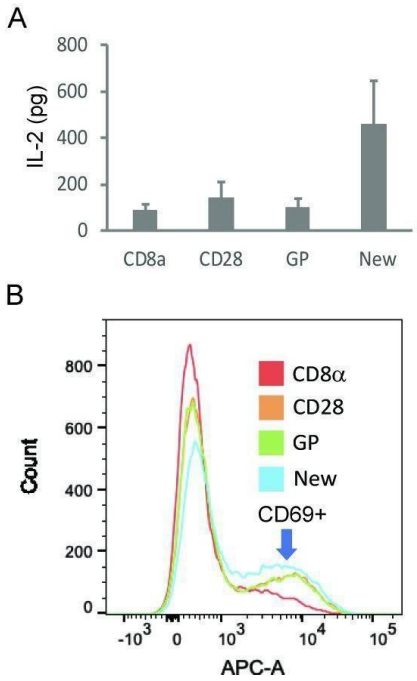
YV7714: Novel Transmembrane Domain to Enhance CAR Activity

Principal Investigator: Xiaolei Su, PhD

- Current CARs are mostly trapped in the intracellular space of T cells. Only a small percentage of CARs are localized to the cell surface.
- Dr. Xiaolei Su's lab at Yale engineered new transmembrane domains that improve the surface localization of CAR and increase CAR T activation.
- The new transmembrane domain could be implemented into CARs targeting a variety of cancer antigens.
- **Intellectual Property:** Patent application pending
- **Reference:** Manuscript in preparation

Figures showing CD19-CAR with the new transmembrane domain induces higher IL-2 production and CD69 expression as compared to the conv entional CD8a or CD28 transmembrane domain.



Yale
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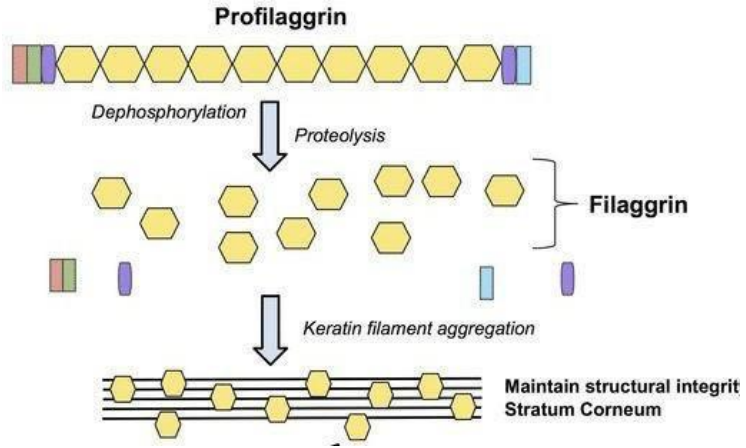
YV7416: Novel Topical Peptide Therapeutics and Moisturizers

Principal Investigator: Christopher Bunick, M.D., Ph.D.

Filaggrin-Keratin Complex in Skin Protection and Treatment

- 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.
- Currently, all the topical moisturizers on the market focus on lipid replenishment, prevention of water loss, and water absorption methods, or utilize FLG at the stage of final breakdown (natural moisturizing factor, NMF) – this is post-keratin binding and therefore has limited efficacy.
- We have identified two specific short segments of FLG that are critical for keratin aggregation. We are developing novel peptide-based agents that promote promote K macrofibril formation; these can serve as novel treatment for atopical dermatitis, ichthyosis, psoriasis, and other skin conditions, as well as basis for new types of skin moisturizers.
- **IP Status:** PRV application filed in 2018



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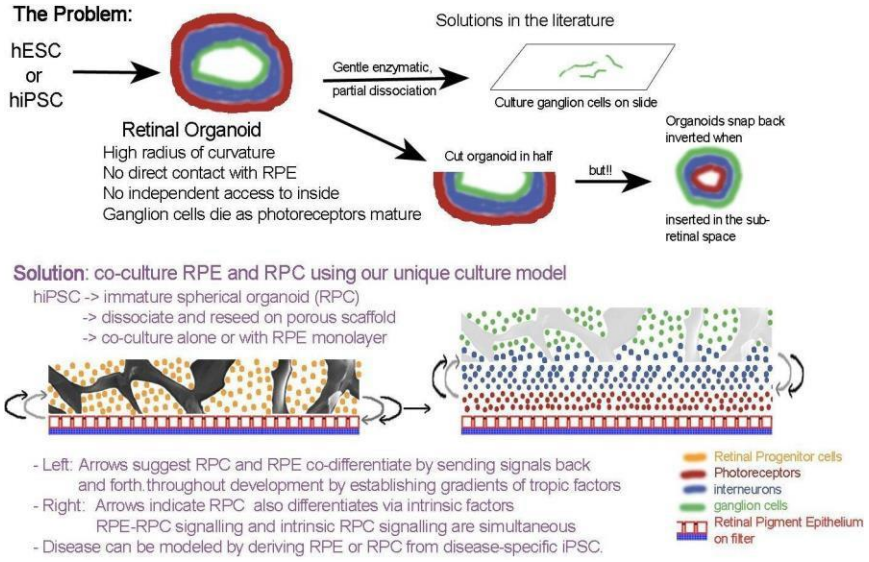
YV7254: Planar Retinal Organoid

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.

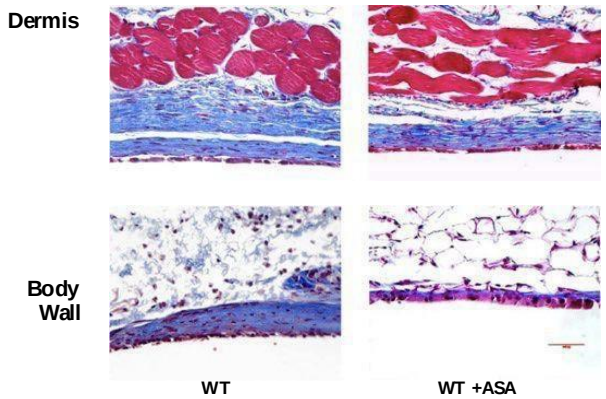
- **IP status:** 17/845,461 **pending**
- **Reference:** Biomaterials 2018, 154: 158-168

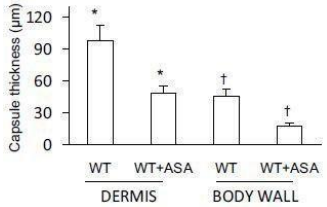


YV5199: Foreign Body Rejection

Principal Investigator: Wajahat Mehal, MD, DPhil

- Implantation of biomaterials and devices into soft tissues leads to the development of the foreign body response (FBR), which can interfere with implant function and eventually lead to failure – currently there are no therapeutic options.
- We show that the acute inflammatory response to biomaterials can be limited by inhibition of inflammasome-related pathways.
- Aspirin reduces significantly reduces the FBR in response to silicone implants, as shown in figures (*†P ≤ 0.05)
- Advantages:
  - Improve the function of biomaterials
  - Reduce the need to replace biomaterials and devices
  - Reduce side effects from inflammation related to biomaterials
- **IP status: issued** US Patent No. 9,415,046





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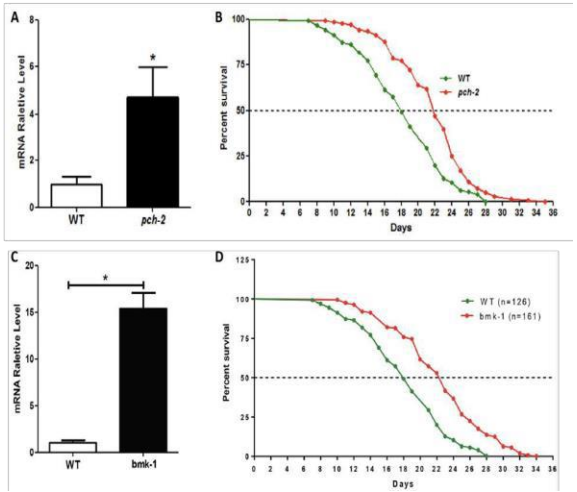
YV5132: Anti-Aging

Principal Investigator: Laura Niklason

A new method to increase longevity or treating cellular stress

- Over-expressing either pch-2 or bmk-1 in C. elegans by microinjection extends worm lifespan by ~25% and enhances worm survival survival in response to various stressors including oxidation, apoptosis and DNA damage.
- Inhibition of either gene by RNAi results in shortened lifespan. Moreover, the over-expression of the human equivalents of these two genes in cultured fibroblasts confers resistance to environmental stressors, and promotes cell survival after exposure to radiation or oxidative stress.
- **Patent:** US Patent Issued.
- **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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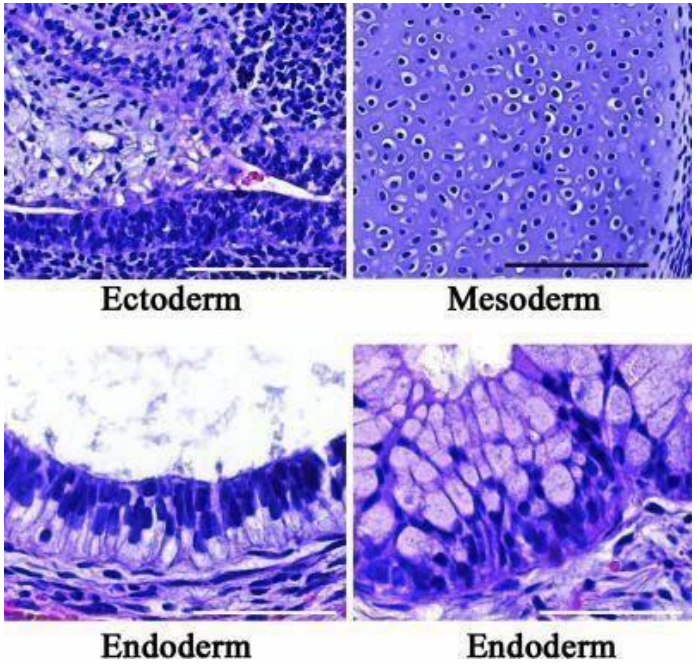
YV4056: Stem Cell Culture Medium

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
- Issued US Patent & Reference



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YV8103: Spatiotemporal Control of CRISPR-Cas Binding

Principal Investigator: Peter Glazer, MD, PhD

Background:

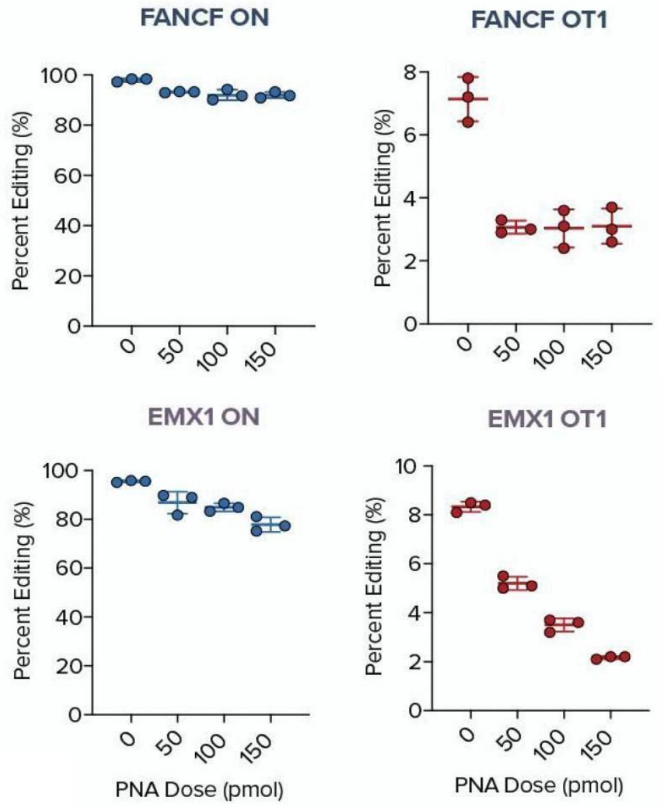
- CRISPR-Cas9 approach is limited by sub-par specificity, causing off-target effects and preventing use in certain indications

Indications: Enhancement of CRISPR therapy

Innovation & Asset: Peptide-nucleic acid (PNA) platform improves upon traditional guide RNAs used in CRISPR

- Increases target specificity
- Potentially allows correction of autosomal dominant disease
- Universally applicable
- Highly potent dosing

IP: Patent application pending



At picomolar doses, administration of the PNA dramatically reduces CRISPR off-target effects (shown in red) with little impact in the on-target effects (shown in blue). Data are presented from both the FANCF gene and the EMX1 gene.

YALE VENTURES

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Yale

YV8224: Human cortical organoids with engineered microglia-like cells

Principal Investigator: In-Hyun Park, PhD

Background:

- Human cortical organoids (hCOs) are valuable models of 3D tissue, but their potential is limited by their lack of mesenchymal components, namely microglia

Indications: Glioblastoma Multiforme (treatment); neurodegenerative & neurodevelopmental disorders (model platform)

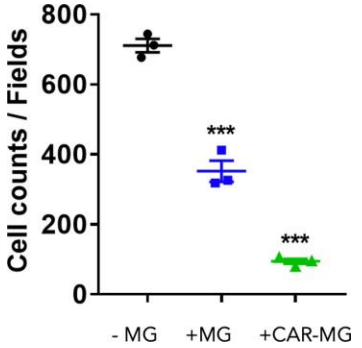
Innovation & Asset: Novel platform to develop microglia-containing hCOs using human embryonic stem cells:

- Tunable, efficient method of microglia generation (Nature publication)
- Microglia may be modified with chimeric antigen receptors (CAR) and used as immunotherapy (A)
- hCOs with microglia allow for improved investigation of numerous brain diseases, including Alzheimer's (B), autism, and schizophrenia

IP: Patent Application Pending

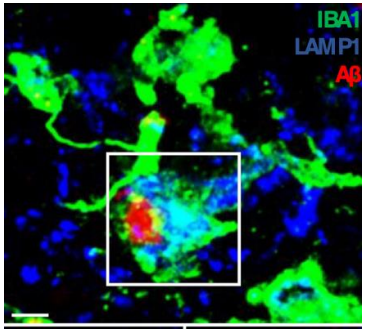
A

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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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

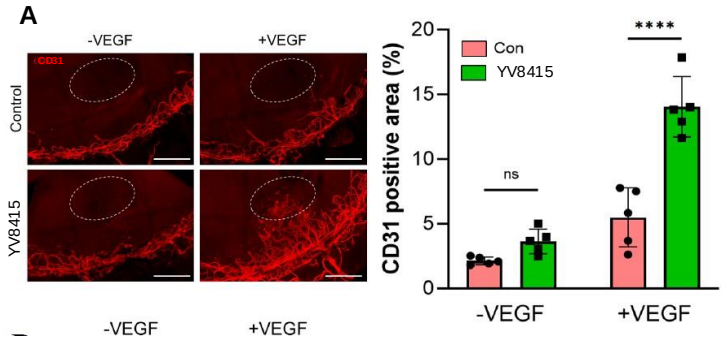
Indications: Wound healing, peripheral arterial disease, critical limb ischemia

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

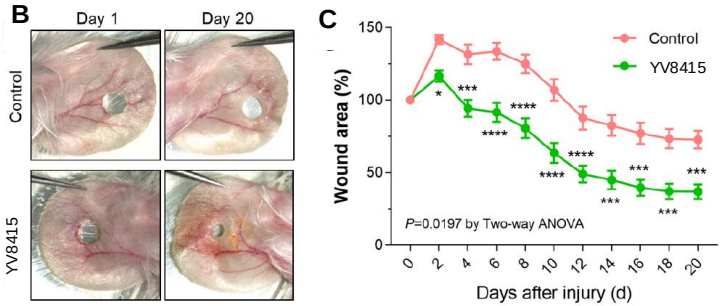
IP: Provisional Patent Filed

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).

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

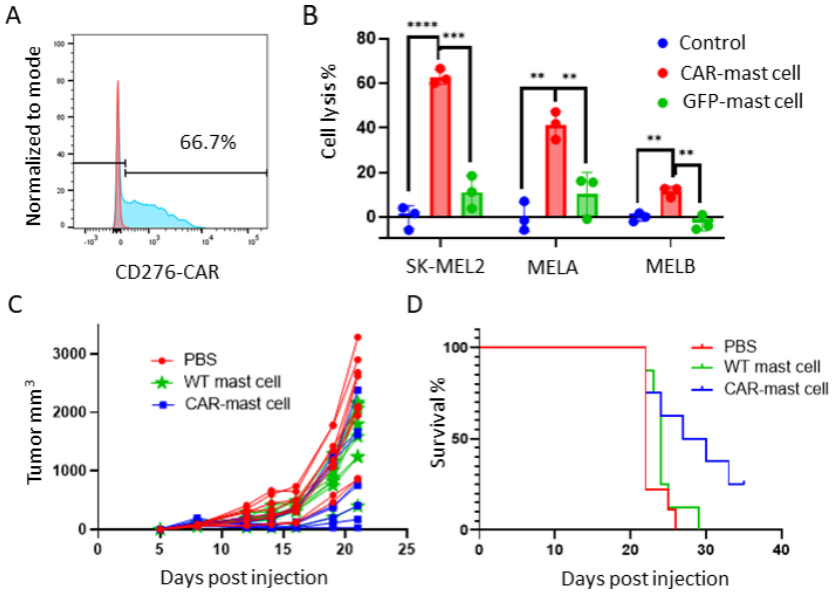


Fig.1 Cytotoxicity of anti-CD276 (B7H3) CAR-mast cells. A) Expression of CD276 CAR in mast cells. **B)** CAR-mast cells were incubated with CD276+ human melanoma cells at an E:T = 5:1. **C)** Monitoring tumor growth in C57BL/6 mice xenografted with MC38-CD276+ cells. Each mouse received 5x10^6 MC38 cells 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

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_v 1.7, a type of Na_v channel, is increased in chondrocytes from people with osteoarthritis (OA)

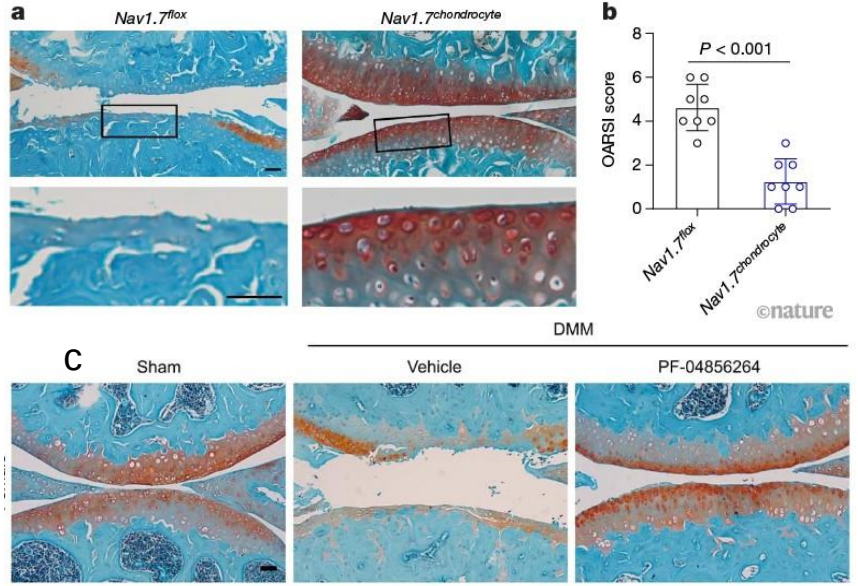
Indications: Osteoarthritis

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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Gene Therapy & Genome Engineering

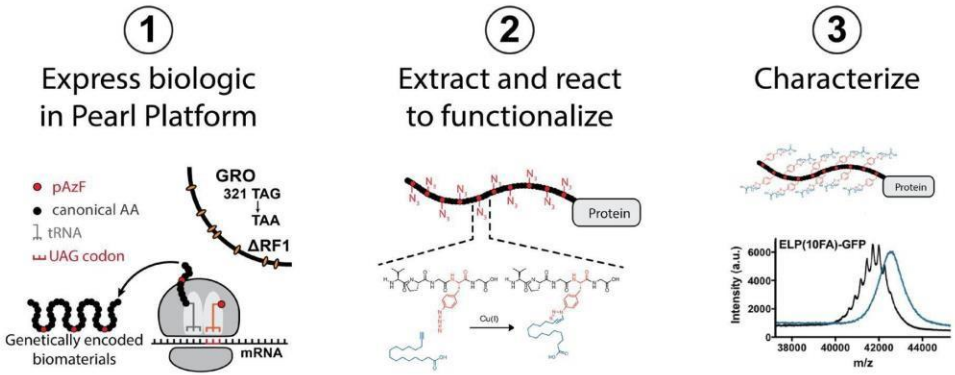
YV: 6349 Precise engineering of protein materials and biologics

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
- 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
- IP

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.

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YV5714: Protein Engineering

Principal Investigator: Dieter Söll

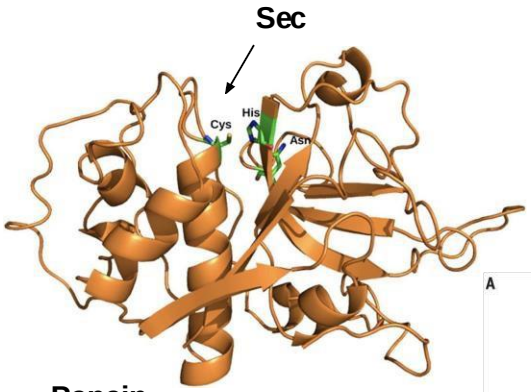
Utility

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



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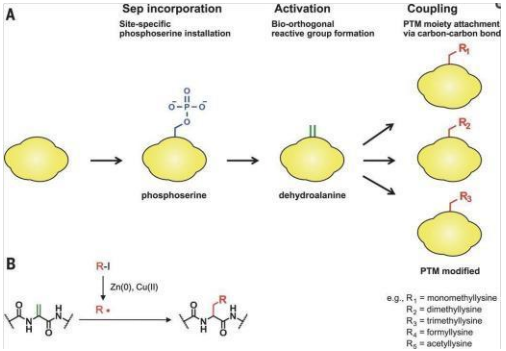


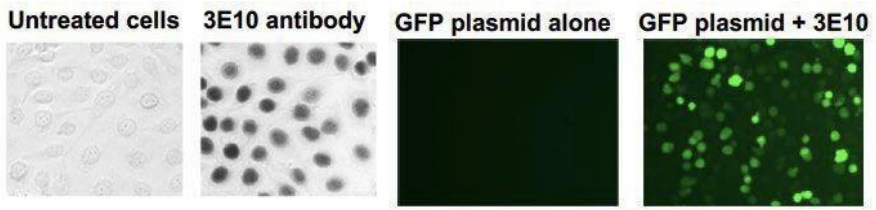
Yang et al (2016) Science 354, 623

YV7503: Antibody-mediated DNA/RNA delivery

PARTNERED

Principal Investigator: Peter Glazer, Ph.D.

- Advantages:
  - No need for DNA cutting or binding agent
  - Patient treatment by simple IV administration of simple mixture of geMab and donor DNA
  - Established manufacturing processes for both components
  - The approach has no sequence limitations to reagent design
- Therapeutic applications. Gene editing to correct mutations causing genetic disorders: sickle cell disease, thalassemia, cystic fibrosis, lysosome storage diseases
- **IP status:** pending "COMPOSITIONS AND METHODS FOR ENHANCING DONOR OLIGONUCLEOTIDE BASED GENE EDITING"



3E10 is a cell penetrating mAb that transports a donor DNA for gene editing into cells and tissues in vivo

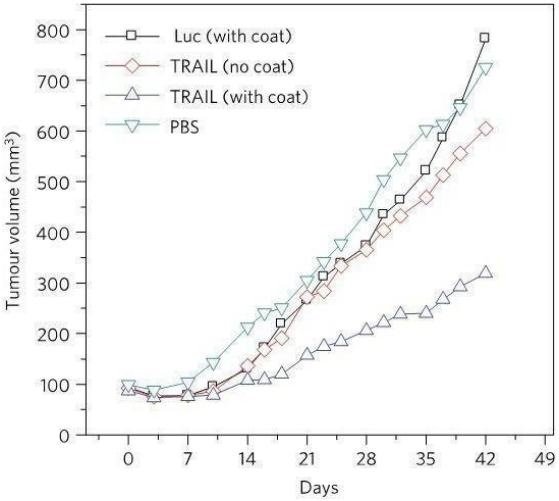
YV4902/5543/6951/6195: Nanoparticles for Controlled Delivery of Nucleic Acids

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



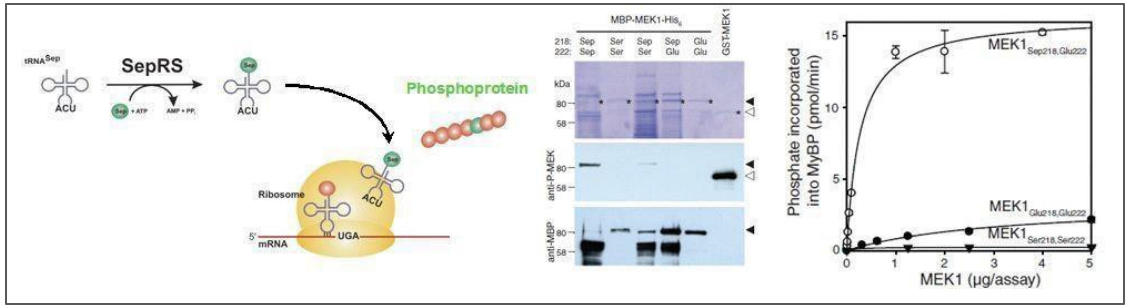
Tumor size in mice treatedwith nanoparticle-coated TRAIL (proapoptotic gene) w as significantly smaller than that in mice treated with no-coatTRAIL or saline.

YV3105: Site-Specific Insertion of Phospho-AA

Principal Investigator: Dieter Söll

Site-Specific Efficient Incorporation of Phosphoserine into Proteins Using a Novel EF-Tu and tRNA Charging System

- In general, phosphoproteins are highlyunstable anddifficult to produce.
- YV3105/5254 pertains to the creation of a simple tool kit for the efficient site specific, phosphorylation signal-independent, introduction of phosphoserine into proteins in vitro and in vivo using a novel vector compatible with complementary bacterial strains and mammalian tissue culture.
- This technologyprovides a method of site specific cotranslational incorporation of phosphoserine into proteins, including human MEK-1.
- The production of phosphoprotein is inducible byphosphoserine and the system is compatible with transgenic methodologies.
- Applications:
  - research tools for the studyof kinases and phosphatases
  - development of cell-based screens for new drug discovery
  - the manufacture of phosphoproteins for applications such as antibody generation
  - protein array manufacture
  - the target proteins in signal transduction pathways
- Issued Patent & Reference



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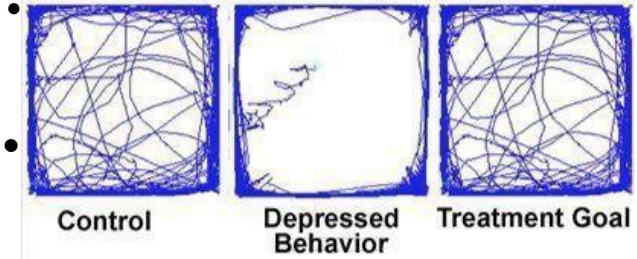
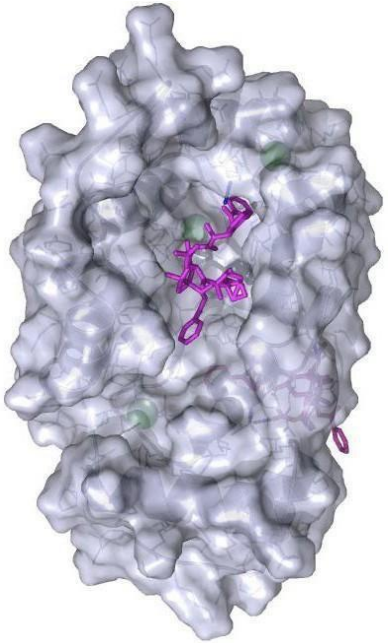
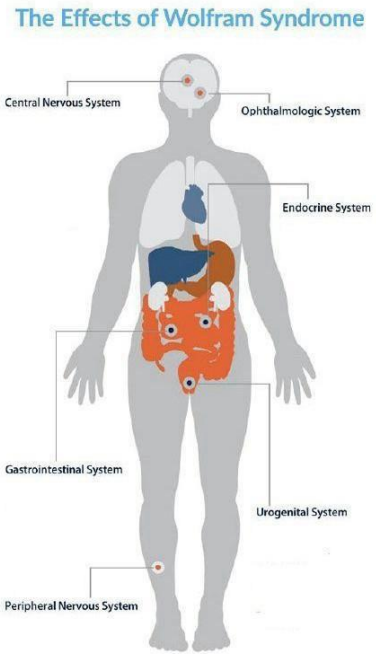
Orphan & Rare Diseases

YV7709: Novel Druggable Targetfor 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
- 





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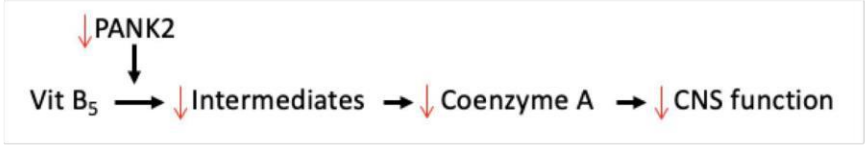
YV7653 & YV7903: PANK3 Activation for Pantothenate Kinase-Associated Neurodegeneration (PKAN)

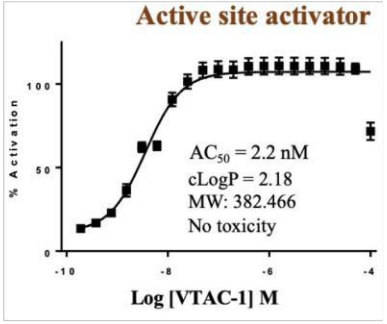
Principal Investigator: Choukri Ben Mamoun, PhD

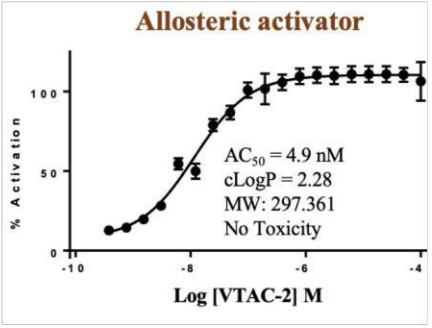
- **Background:** Pantothenate Kinase-Associated Neurodegeneration (PKAN)
  - Neurodegenerative disease caused by autosomal recessive LOF in PANK2 gene (**A**)
  - Estimated 320-1000 patients in USA
  - No disease modifying therapy
- **Innovation & Asset:** Highly potent activators of human PANK3 isoform 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:

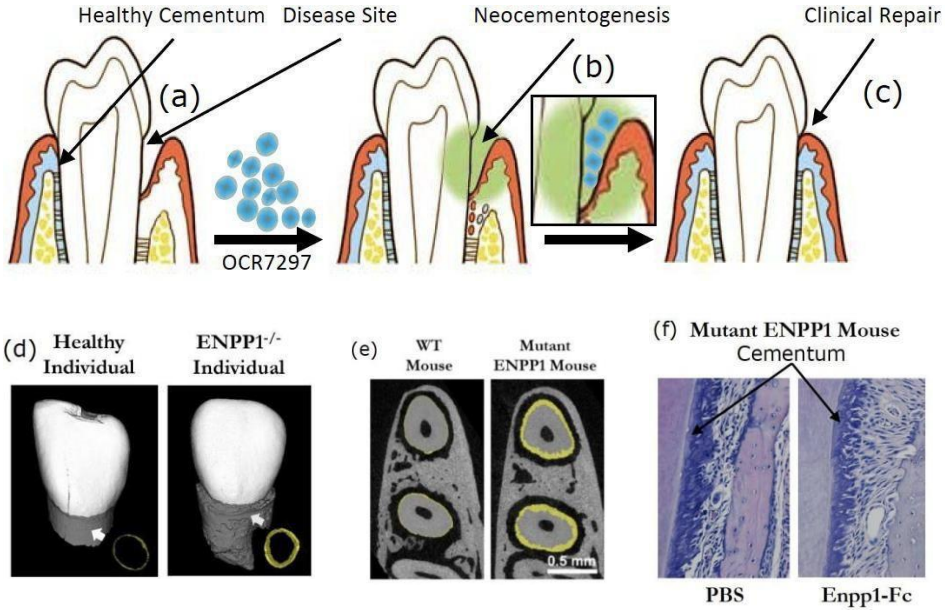
- **Human:** ENPP1 loss Hypercementosis (d)
- **Mouse:** Mutant ENPP1 Hypercementosis (e)
- **Mouse:** Enpp1-Fc reduces cementum (f)

Therapeutic/Regulatory Approach:

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

IP: Patent Pending

Cementum Loss Promotes Periodontal Disease



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YALE VENTURES

YV6436: Treatment for Osteogenesis Imperfecta

Principal Investigator: Chuhan Chung

PEDF and Derivative Peptide for Treatment of Osteogenesis Imperfecta

- Absence of pigment epithelium- derived factor (PEDF) causes Osteogenesis Imperfecta (OI) in humans.
- OI Type VI is an autosomal recessive disease manifested by severely impaired bone mineralization and fractures in early childhood.
- PEDF is a regulator of MSC differentiation to the osteoblast lineage. PEDF modulates Wnt/β- catenin signaling to direct MSC fate toward osteoblasts. Restoration of PEDF in this PEDF KO mice corrected the bone phenotype (figure).
- Recently it was shown that PEDF treatment restores bone elasticity and reduces bone brittleness in the PEDF-KO mouse model (Unpublished data).
- **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.
- **Intellectual Property:** US patent issued No. 10,357,549

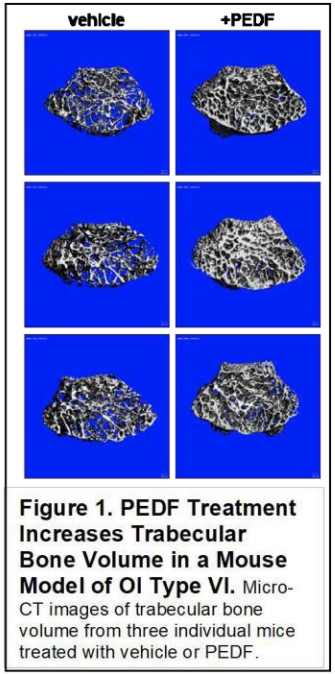


Figure 1. PEDF Treatment Increases Trabecular Bone Volume in a Mouse Model of OI Type VI. Micro-CT images of trabecular bone volume from three individual mice treated with vehicle or PEDF.

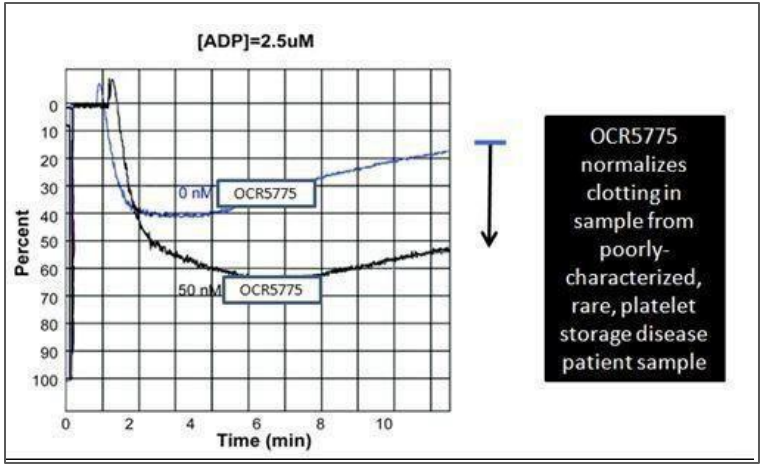
YV5775: Clotting Disorders

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 only at sites of platelet degranulation triggered under physiological conditions (i.e. response to vascular damage)
- As shown in the figure, weak aggregation is seen in 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 a critical care situation such as [illegible] Department for acute bleeding episodes (e.g., NSAID toxicity), first response, or military situations.



Several Issued Patents & Reference

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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).

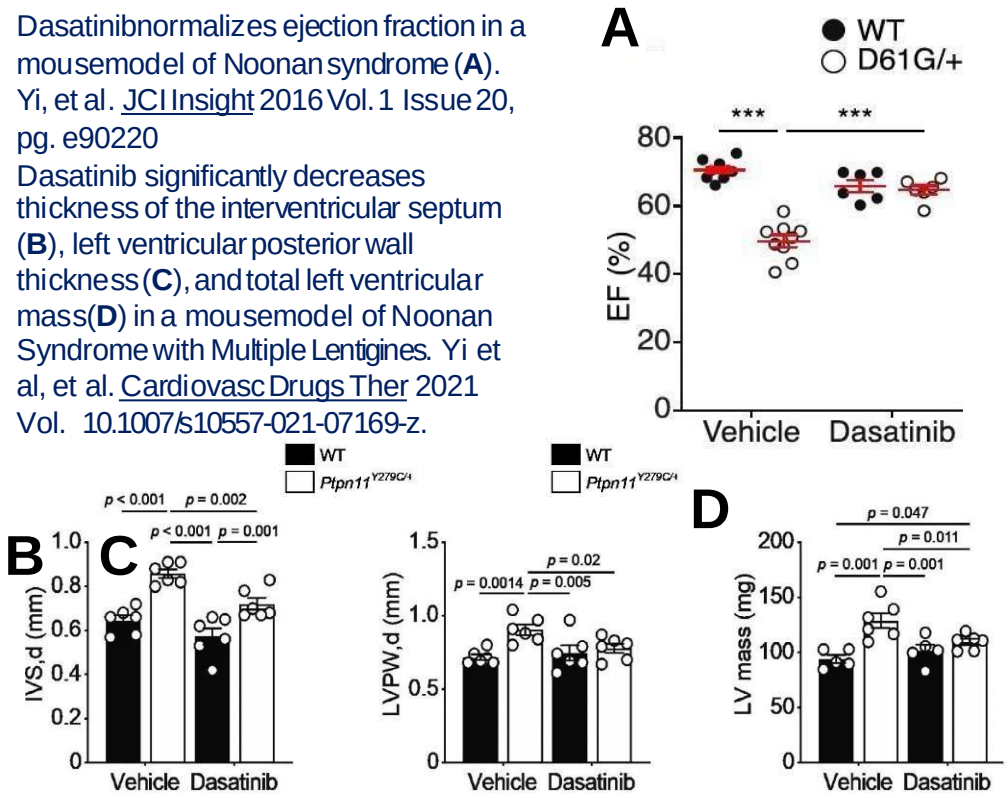
Innovation & Asset: Low-dosetyrosine kinase inhibitor therapy (dasatinib, trametinib).

- 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

Intellectual Property:

- Low-Dose Kinase Inhibitors.
- Formulation for Pediatric Use.

Dasatinibnormalizes ejection fraction in a mousemodel of Noonan syndrome (**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

Drug delivery:

Nanoparticles, Topical Technology & Sustained Delivery

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

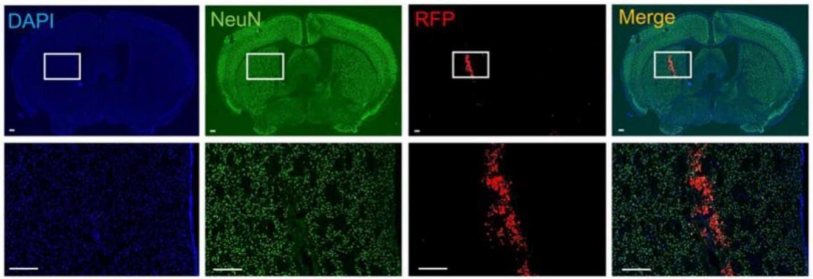
Innovation & Asset: Cytoplasm-localizing anti-Guanosine [or Guanine] antibody, 4H2:

- 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

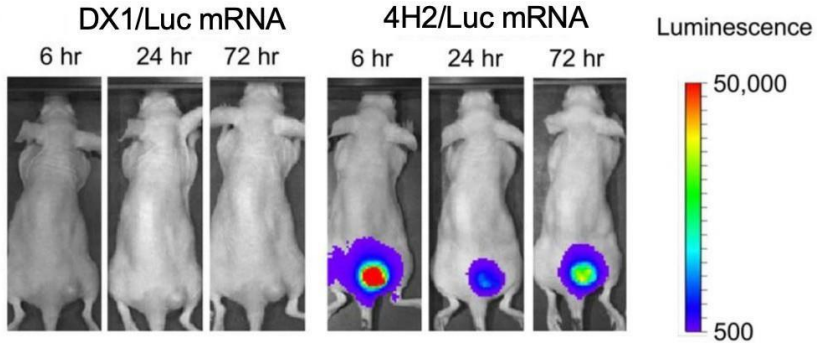
A

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 local area 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.



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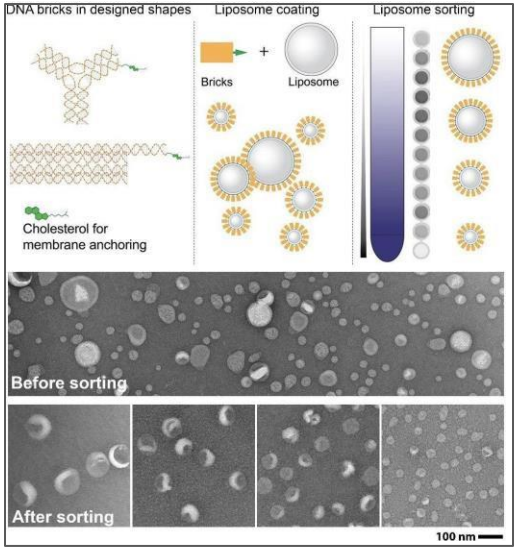
YV7861: DNA-brick assisted liposome sorting

Principal Investigator: Chenxiang Lin

- Size-controlled liposomes are essential for basic research and biotechnology. Current liposome homogenization methods lack precision, versatility, and/or scalability.
- Dr. Chenxiang Lin's lab at Yale invented a method to sort heterogeneous liposomes into a wide range of uniformly-sized populations by DNA-brick assisted density-gradient centrifugation.
- Sorting is effective on premade liposomes with various sizes and contents. Protein and nucleic-acid cargos retain their functions after sorting.
- The method is useful for the study of membrane biophysics and for formulation and prototyping of liposomal drug-carrying vehicles.
- **Intellectual Property:** Patent application pending
- **Reference:** BioRxiv (2020.02.01.930321v1)



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

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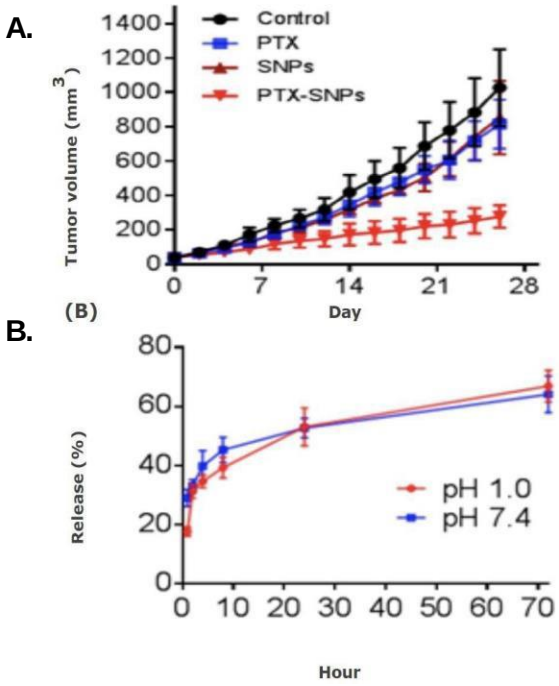
YV7119: Nanomaterial technology to enable efficient oral drug delivery

PARTNERED

Principal Investigator: Jiangbing Zhou

- Supramolecular nanoparticles (SNPs) that effectively enhance the oral bioavailability of cargo drugs;
- Functional nano- or microstructures from five classes of MNPs and their synthetic analogs and derivatives are stable in strong acidic environment (as low as pH 1.0) and can effectively penetrate the gastrointestinal tract;
- Small compound chemotherapeutic agents and peptide therapeutics encapsulated therein show a much greater plasma concentration and targeted tissue adsorption following oral administration and strong efficacy in treating tumors, diabetes, and stroke in animal models.
- **Intellectual Property:** US Patent Application Pending



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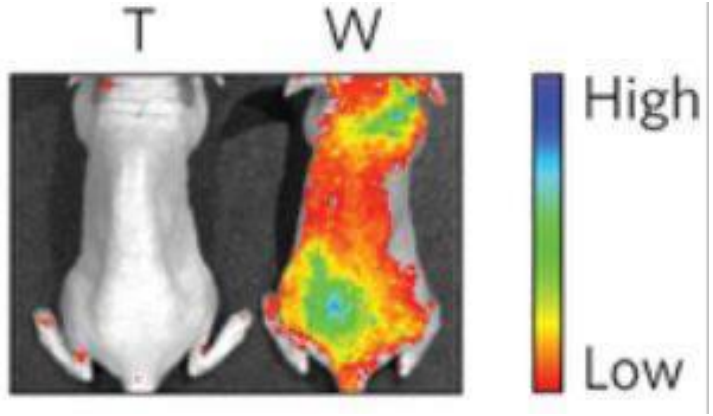
YV6839/6688: Adhesive, Non-absorbent Nanoparticles for Dermal Applications

PARTNERED

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

Adhesive, Non-absorbent Nanoparticles for Dermal Applications

- 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 with Xenogen. Deng et al. (2015). Nature Materials

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

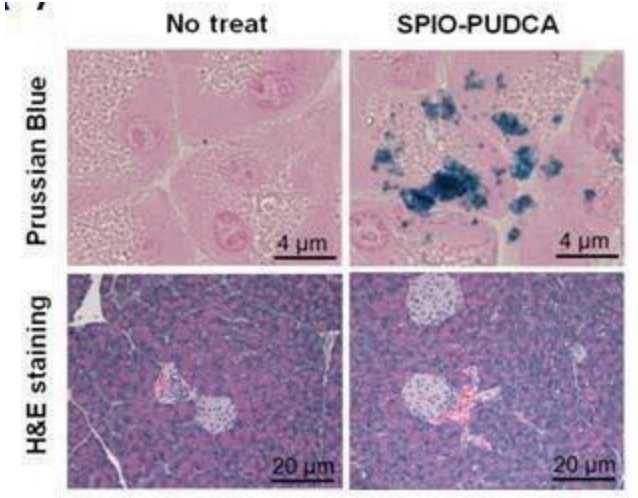


FIG. Histologyimages of pancreatic sections from mice that were orally treated with PBS or PUDCAnanoparticles containing iron oxide (SPIO-PUDCA). Iron Oxide is assayed using the Prussian Blue stain which appears distinct in the pancreas.

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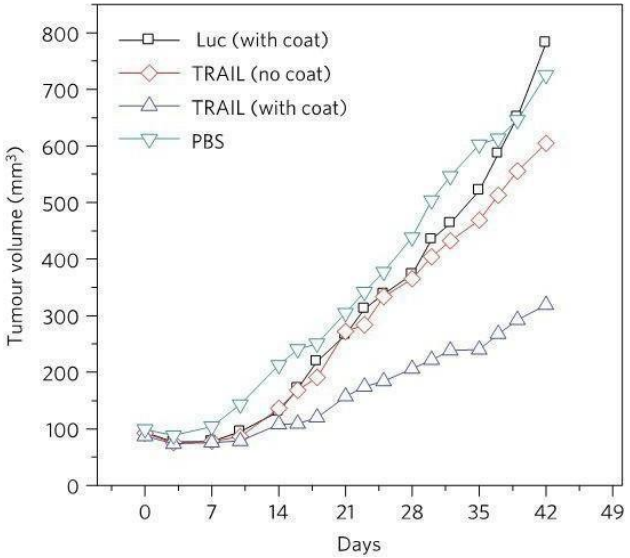
YV4902/5543/6951/6195: Nanoparticles for Controlled Delivery of Nucleic Acids

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.

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YV8728: Sequencing & Targeting of Nucleotide Repeat Expansion RNAs

Principal Investigator: Junjie Guo, PhD

Background:

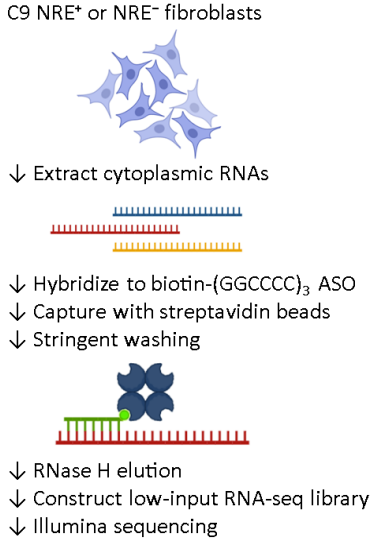
- Nucleotide Repeat Expansions (NRE) cause 40+ human diseases
- NRE-containing RNAs are difficult to sequence and to selectively target with oligonucleotide drugs

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

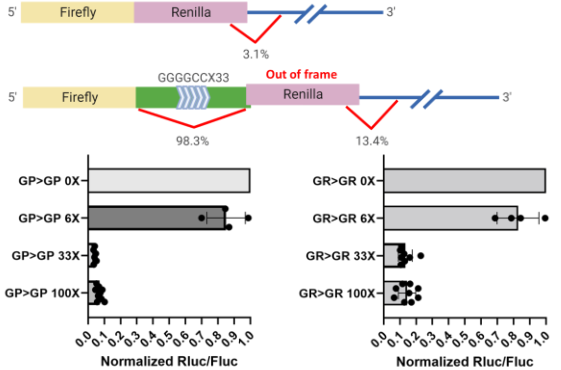
Innovation & Asset: Novel, generalizable method allows for the following:

- Sequencing NRE-containing RNA (A)
- Modeling NRE-induced aberrant splicing (B)
- Targeting NRE-containing RNA (C)
- Demonstrated efficacy investigating & targeting $(GGGGCC)_n$ repeats of C9orf72 gene in ALS/FTD

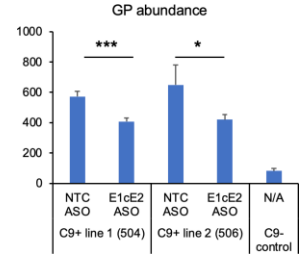
A Novel process of selectively sequencing NRE+ C9orf72 RNA from human fibroblasts



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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Diagnostics/ Biomarkers/Imaging

YV 4925: Early Detection of β cell death

PARTNERED

Principal Investigator: Kevan Herold

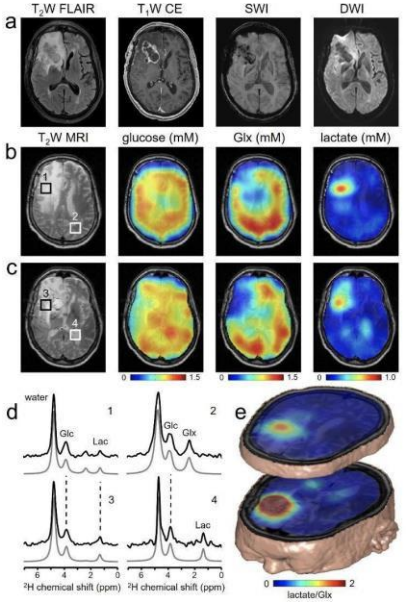
Detection of β cell death in diabetes using differentially methylated circulating DNA

- A powerful biomarker and diagnostic indictors have been identified for ongoing β cell death in diabetic patient;
- A method of measure such marker has beendeveloped
- **Reference:** Proc Natl Acad Sci U S A. 2011 Nov 22;108(47):19018-23
- **Intellectual Property:** US and Europeanpatents are issued

YV7350: Novel Deuterium Metabolic Imaging (Dmi)

Principal Investigators: Henk De-Feyter, PhD, Robin de Graaf, PhD

- We developed novel magnetic resonance-based imaging technique
- Provides **3D maps of active metabolism in 20 min** scan.
- Detects metabolism of nutrients/substrates such as glucose or acetate labeled with the stable isotope deuterium (2H).
- Can be easily implemented on existing **3T and 7T MRI scanners;** very robust method: potential for push-button imaging.
- Substrates: 2H-labeled substrates and nutrients are commercially available and affordable.
- DMI has been performed in **animals and humans,** using 2Hglucose and 2H-acetate, imaging **brain and liver metabolism.**
- After an oral dose of 2H-labeled glucose, DMI provided unprecedented image contrast based on glucose metabolism in a patient with GBM brain tumor.
- Can be applied in other organs and tissues and to any pathology, intervention or treatment with a metabolic component.
- **IP status: US 62/608,861 pending**



DMI visualizes the Warburg effect in a patient with GBM after oral 2H-glucose intake. a) Clinical MR images acquired in a patient diagnosed with GBM in the right frontal lobe. b, c) T2-weighted MRI and overlaid DMI maps in two slices that contain the tumor lesion. The MRI and DMI data shown in (c) correspond to the slice position of the clinical MR scans in (a). DMI maps show homogenous distribution of 2H-glucose across the slices but lower levels of 2H-labeled glutamate+glutamine (Glx) and a higher concentration of 2H-labeled lactate in the tumor lesion compared to normal-appearing brain. d) 2H NMR spectra from selected locations depicted in the T2W MR image, including tissue (1, 3) within the lesion as seen on T1W CE; (2) from normal-appearing occipital lobe and (4 containing glucose and lactate from the lateral ventricle. e) 3D illustration of combined MRI and DMI of the lactate/Glx ratio representing the spatial distribution of the Warburg effect.

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YALE VENTURES

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

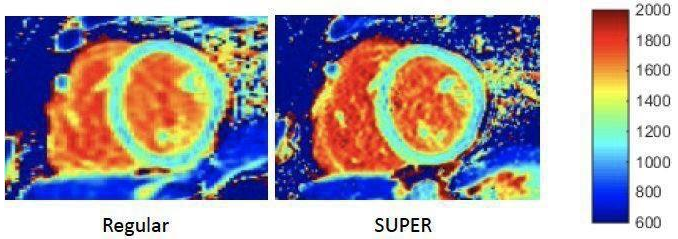

Figure 1: Image comparison: the same time is used, the image resolution doubles

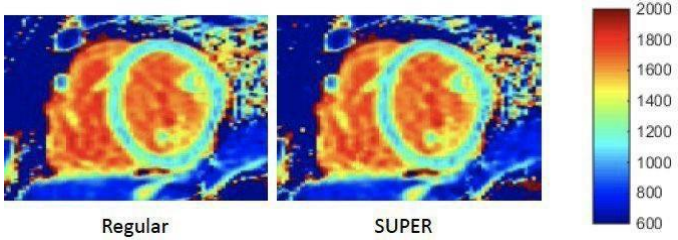

Figure 2. Image comparison: time is reduced un SUPER, while image quality is retained

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YALE VENTURES

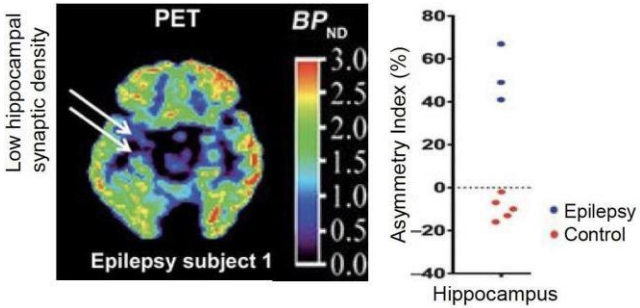
YV7160: Radiopharmaceuticals for synaptic imaging

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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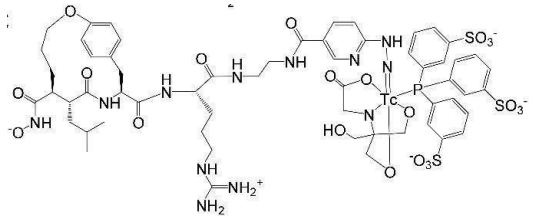
YV6966: MMP-associated Inhibitors and Tracers

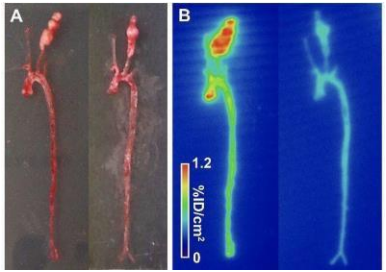
Principal Investigator: Mehran Sadeghi

Novel matrix metalloproteinases (MMPs) Inhibitor and MMPtargeted 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.
- Currently there 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 display improved pharmacokinetics and water solubility as compared to previously reported MMP SEPCT probes (i.e. RP805)
- Intellectual Property

Novel MMP inhibitor and MMPtargeted imaging tracer 99mTc-RYM1





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

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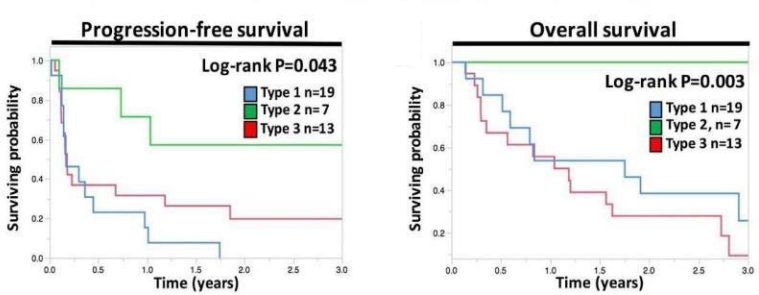
YV6922: Selection of Non Small Cell Lung Cancer Patients Responsive to Checkpoint Inhibitors

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.
- **Intellectual Property**



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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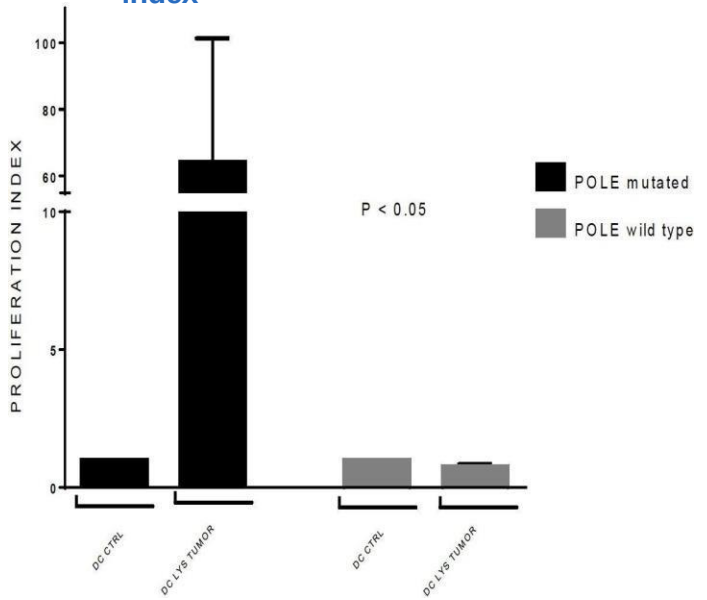
YV6104: Tumor Biomarker for Prognosis of Response to Immunotherapy

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).

Priming CD4+ pro life ration index



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YALE VENTURES

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

YV8097: Tracers for Imaging Collagen Turnover

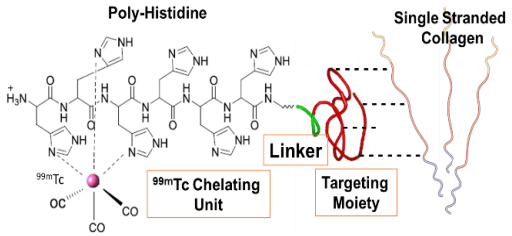
Principal Investigator: Mehran M. Sadeghi, MD

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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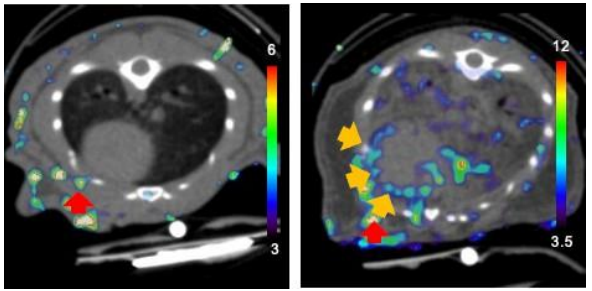


Examples of SPECT/CT images acquired at 2 hours post injection of ^{99m}Tc-His6-$(GPO)_9$ in mice at 5 days after LAD occlusion (right) and sham operation (left) demonstrating uptake of the tracer in the anterior and lateral myocardium (orange arrows). Cutaneous uptake, probably related to surgery, is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

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

- Uniquely targets denatured 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)

Devices, Methods, Models & Assays

YV8519: Novel methods of human microbiota genotoxin analysis

Principal Investigator: Noah Palm, PhD

Background: Small molecule metabolites of the gut microbiome may increase colorectal cancer (CRC) risk

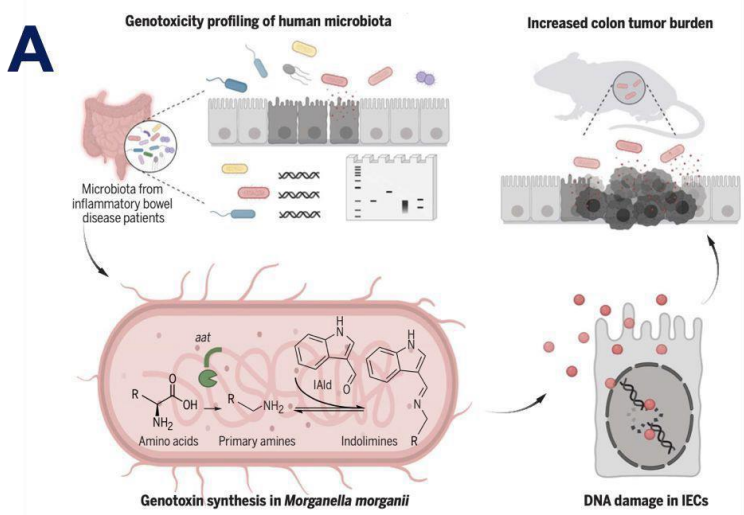
- Current approaches of metagenomics and 16s rRNA sequencing do not provide directly causal information about DNA damage

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

Innovation & Asset: Novel CRC target family & large-scale method for identificationof other genotoxic microbes, strains or metabolites thereof

- Systemic approach that provides causal, mechanistic information about DNA damage
- Demonstrated efficacy via discovery of novel genotoxin family (indolimines) in *M. morganii* (**A**)
- *Full Publication in Science*

IP: Patent application pending



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.

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YV8510: Novel Wet Adhesives Derived from Bacterial Biofilm

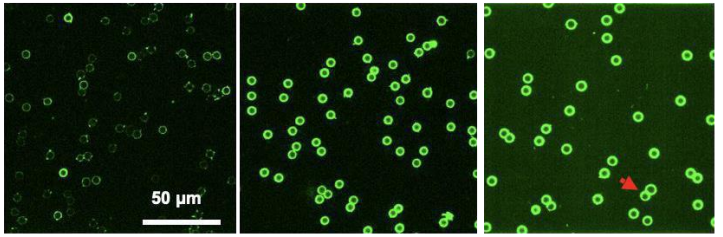
Principal Investigator: Jing Yan, PhD & Rich Olson, PhD

Background: Adhesive materials in wet environments

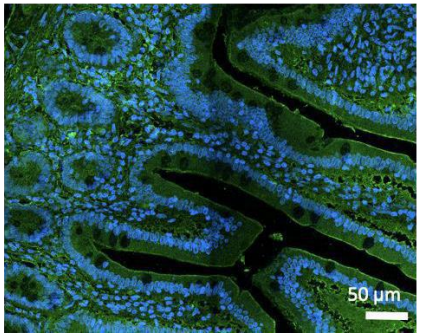
- Current options are limited in efficacy and are sensitive to changes in oxygen & pH levels
- Novel biofilm derivatives demonstrate adhesion **Indications:** Underwater engineering (ship materials, underwater vehicles, etc.) & biological applications (catheters, stents, bone repair, grafts, heart valves, etc.) **Innovation & Asset:** Bio-adhesives derived from Vibrio biofilm
- Multiple sequence variations allow for abiotic (A) and biotic (B) applications
- May be integrated with other recombinant proteins
- Simple mass production via chemical synthesis or bacterial expression
- Stable in various environments

IP: Patent application pending

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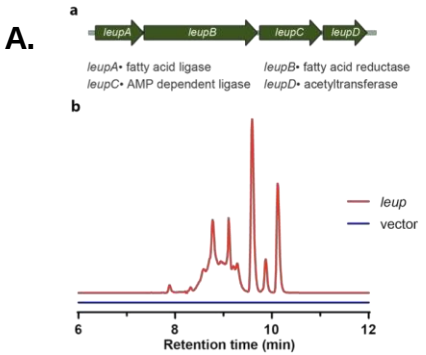
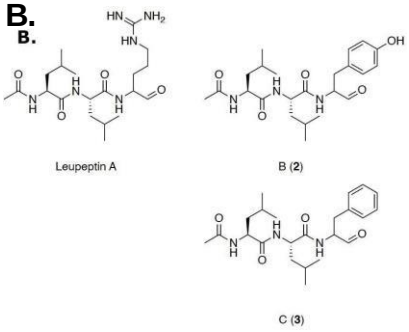
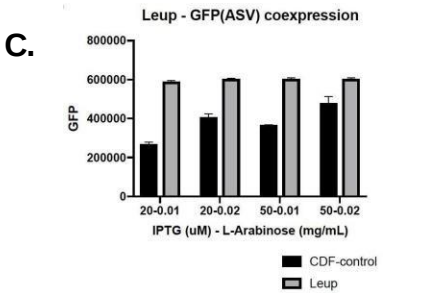
YV7917: System for Enhanced Production of Leupeptins in E. coli

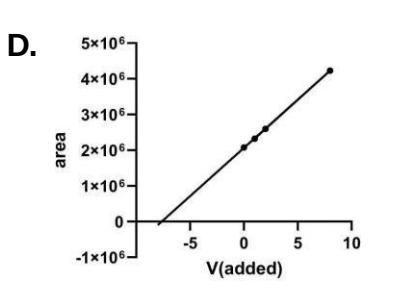
Principal Investigator: Jason Crawford & Lab Interests

- **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***
  - 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**
  - **Pending Patent**
  - Compositions, methods of manufacture and uses.
    - Heterologous production in E. coli
    - Engineering the pathway for leupeptin B, C production









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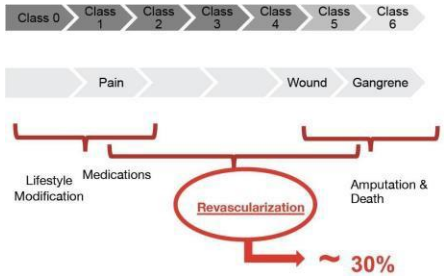
YV7894: Multidirectional Sheath for PAD

Principal Investigator:

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

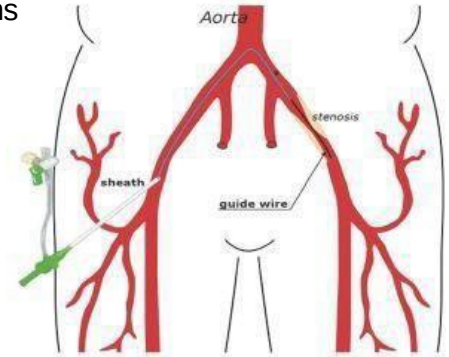
- PAD Patients > 200 million worldwide Majority are over age 65 (double by 2040)
- ~900,000 PAD procedures per year
- ~ 57% are reinterventions



Current Practice for all PAD procedures (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)
- ↓ Total number of interventions & use of closure devices
- ↓ Access site complications by **50%**
- Projected Sheath Cost per unit (~ $150)



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YALE VENTURES

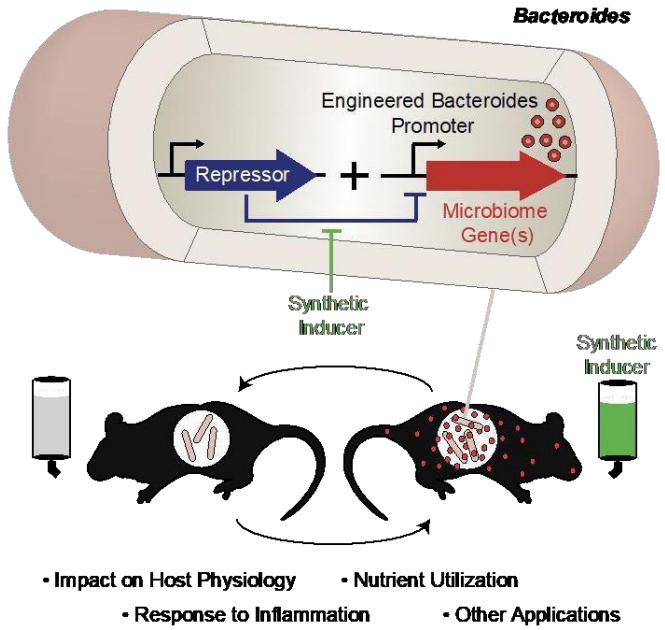
YV7209: Inducible gene expression system for commensal bacteria

Principal Investigator: Andrew Goodman

- A powerful and versatile gene expression system for Bacteroides, the most common genus of bacteria in the human gut.
- Expression of the gene-of-interest can be induced 5 orders of magnitude above background
- Works in the 11 Bacteroides species tested.
- Works in mice solely colonized with the modified Bacteroides and mice carrying the modified Bacteroides with a complete microbial community.
- Can be potentially used to deliver therapeutic agents through commensal bacteria as well as a research tool.

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

- **Intellectual Property:** US Patent Issued



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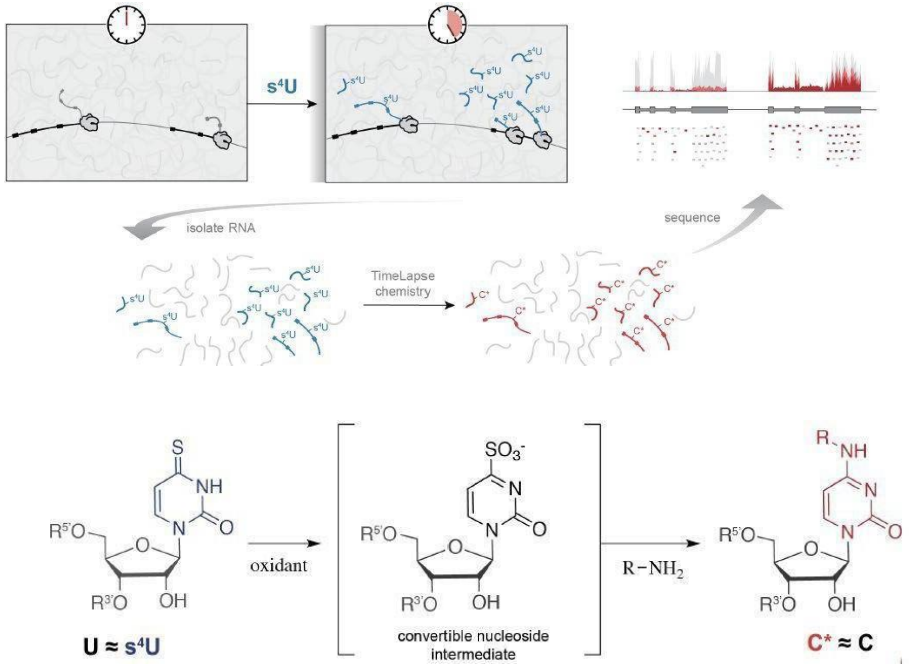
YV7187: Time Lapse Sequencing

Enrichment-free analysis of temporal dynamics of RNA

- Ability to monitor global steady state RNA turnover and distinguish acute transcriptional changes.
- Allows for the identification of isoform-specific transcript dynamics.
- Tags new transcripts with 4-thiouridine (s4U).
- 4-thiouridine is converted to into cytidine analogs which leads to U-C mutations and marks new transcripts upon sequencing.
- Broadly applicable to any application with metabolic labeling.



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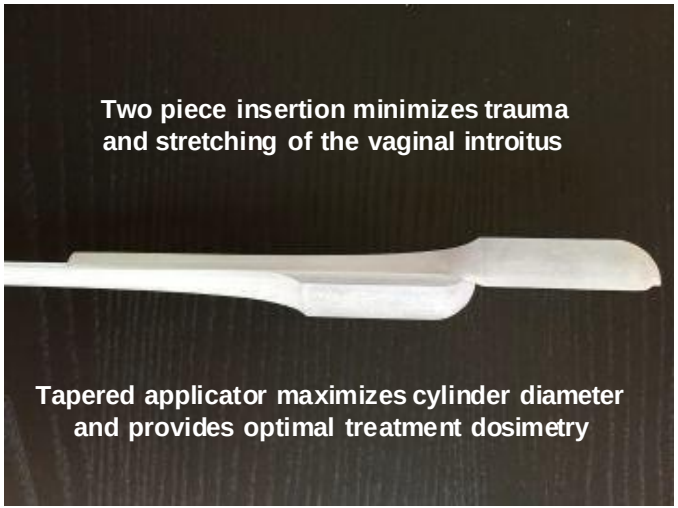
YV7116: Yale Tapered Applicator for Improved Intravaginal Brachytherapy

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

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

- There are an estimated 61,380 new cases of endometrial cancer every year, typically in post-menopausal women.
- Standard treatment of endometrial cancer after surgery requires the direct application of radiation internally (known as “intravaginal brachytherapy”).
- Ideal radiation treatment occurs when the largest diameter of cylinder is used
- Current applicators of radiation therapy are cylindrical, uncomfortable, and limited at times by patient anatomy
- Patient comfort impacts 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 from conventional 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.

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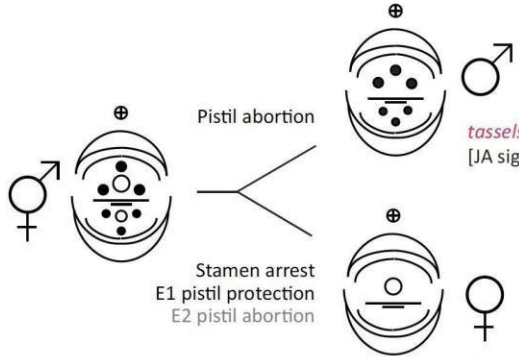
YALE VENTURES

YV7073: Control of sexuality by Sk1 gene

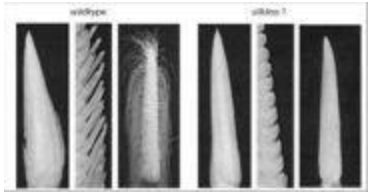
Genotype independent hybrid cereals

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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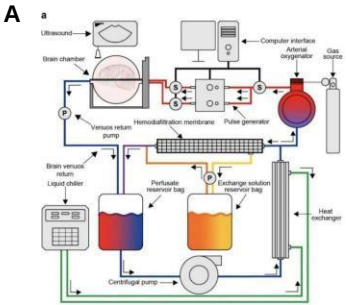
YV7051: Ex Vivo Organ Preservation – Brain, etc.

PARTNERED

Principal Investigator: Sestan Lab

- **Novel Device & Coupled Perfusate**
  - Biomechanicomimetic platform **(A)**
  - Perfusate with a-cellular Hb-based gas exchange, cellular preservation, anti-inflammatory and anti-neurotoxic formulation
  - Multiple organ compatibilities **(B/C)**
    Minimal organ coupling **(B/F)**
- **Ex Vivo Validation-Porcine Brain**
  - 4 hours post-mortem repair and preservation
  - Architecture
    - Global Micro CTA **(D)**
  - Cerebral Metabolism Ultrasound **(E)**
  - Neurotransmission restoration
- **Potential Uses**
  - Ex vivo drug testing (PK/PD, BBB, ADME-T)
  - Ex vivo surgical procedures
  - Transplant organ preservation, reclamation, and assessment
- **Intellectual Property**
- **Request Company Introduction**



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YV6556: Heart Failure Recovery (HFR) Device

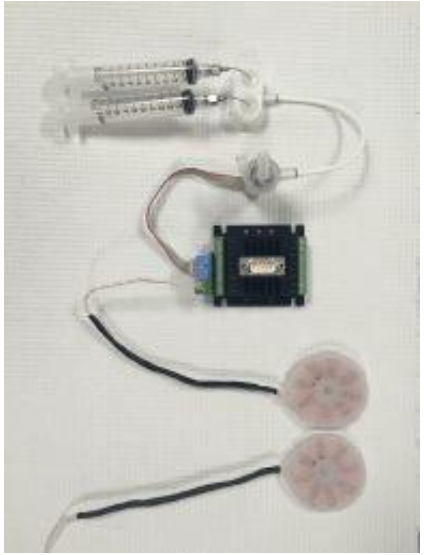
PARTNERED

Principal Investigator:

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.

YV6517: Human Matrix-Polymer Scaffold

Principal Investigator:

PEGylated Amnion scaffold for use in wound management

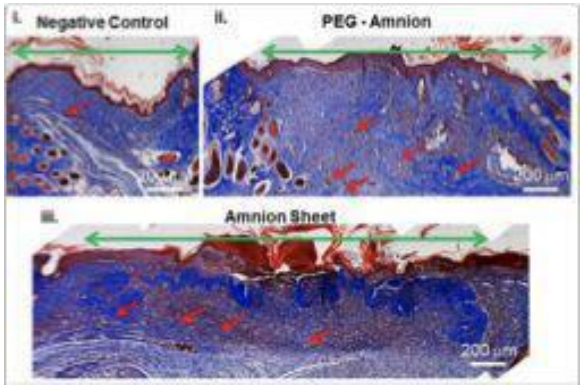
A wound repair hydrogel that combines the benefits of amnion 'scarless healing' with a hydrogel scaffold that conforms to the wound.

Advantages compared with amnion sheet:

- Significantly less wound contraction.
- 2 x faster surface closure.
- Lower infection risk (animal data).
- 8 times less amnion used.
- Utilizes FDA approved materials.
- Conforms to the wound 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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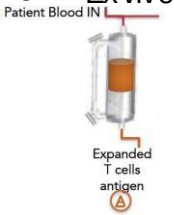
YV4699: T-cell expansion system

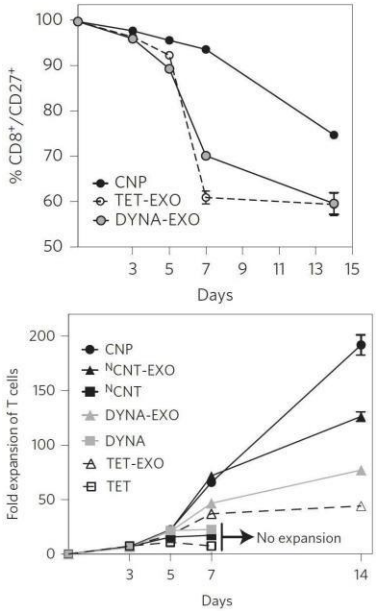
Principal Investigator: Tarek Fahmy, Ph.D.

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 Tcell 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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YALE VENTURES

YV6109: Catalyst-Dependent Synthesis of Glycopeptide Derivatives

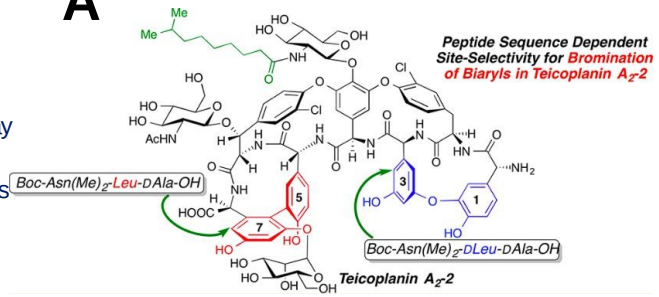
Principal Investigator:

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: Patent: "Site-Selective Functionalization Of Glycopeptide Antibiotics"

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.

Yale

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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 models of 3D tissue, but their potential is limited by their lack of mesenchymal components, namely microglia

Indications: Glioblastoma Multiforme (treatment); neurodegenerative & neurodevelopmental disorders (model platform)

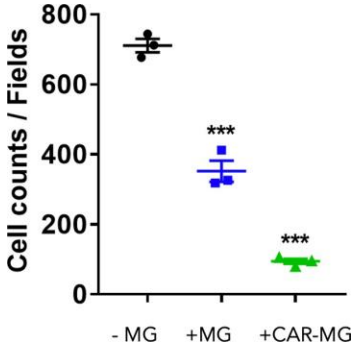
Innovation & Asset: Novel platform to develop microglia-containing hCOs using human embryonic stem cells:

- Tunable, efficient method of microglia generation (Nature publication)
- Microglia may be modified with chimeric antigen receptors (CAR) and used as immunotherapy (A)
- hCOs with microglia allow for improved investigation of numerous brain diseases, including Alzheimer's (B), autism, and schizophrenia

IP: Patent Application Pending

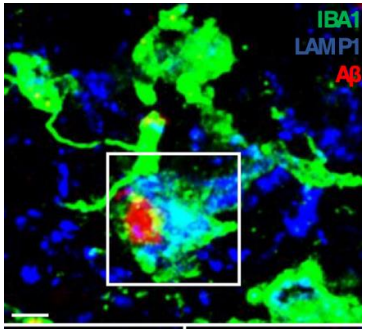
A

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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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)

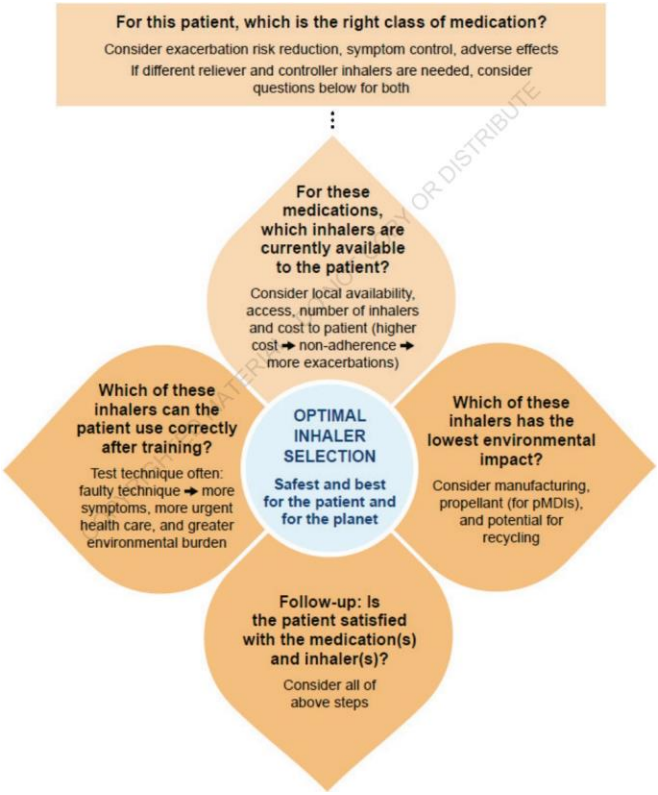

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Image Source: https://ginasthma.org/2023-gina-main-report/

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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

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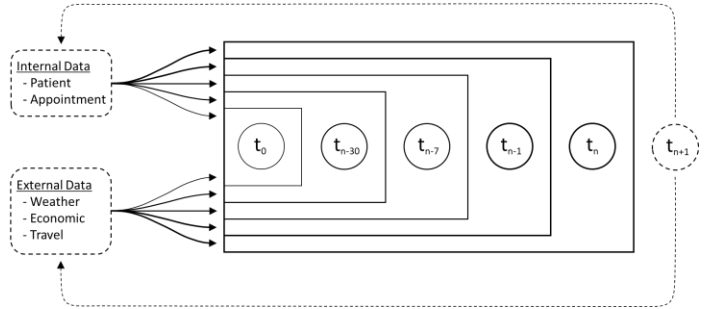
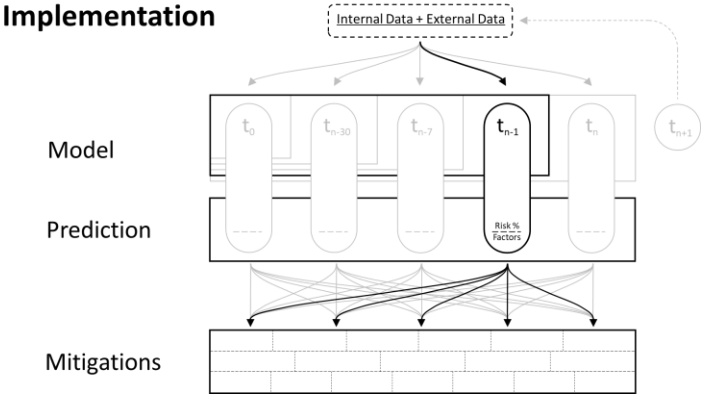
Training



Implementation



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Thank You