Yale University
Innovation Pipeline 2020
Technologies for Partnering
Office of Cooperative Research
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Oncology
OCR6265: Cell Penetrating Anti-Guanosine Antibody Therapeutic for Cancer with Ras Mutations

- **Background:** An antibody has been identified in a mouse model 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

- **Innovator:** James E. Hansen, MD, MS

- **Issued Patents:** US 10,040,867 B2

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

4H2: exemplary cell-penetrating anti-guanosine mAb
A Biomimetic System that Replicates how T-Cells are Expanded in the body

A T-cell expansion method that uses clusters of carbon nanotubes (CNP) to group stimuli together and expand T-cells.

Advantages
• 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*
• And consistently higher than the gold standard Dyna beads – *top figure*
• CNPs are continuously better at T-cell expansion than other methods *in vivo* – *bottom figure*
• Uses 1 ng of reagents for 1 million cells
• Use 1000x less of T-cell growth factor IL-2

Yale Contact: Tarek Fahmy, Ph.D., Yale University School of Engineering and Applied Science
(203) 432-1043, tarek.fahmy@yale.edu
VEGF-C potentiates immunotherapy to eradicate GBM

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

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

**Innovators:**
Akiko Iwasaki, Ph.D.

**Yale Contact:** John Puziss, Ph.D., Yale University Office of Cooperative Research
(203) 785-6167, john.puziss@yale.edu
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.

A PCT patent application has been filed.

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.

Yale Contact: Christopher D. Unsworth, Ph.D., Yale University Office of Cooperative Research
(203) 785-3846, Christopher.unsworth@yale.edu
Targeted Therapy to Solid Tumors

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

- **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 pKₐ 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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**TAP-doxorubicin:** Same efficacy at NOAEL as doxorubicin at MTD

- **YU244206 100 mg/kg**
- **YU241531 100 mg/kg**
- **Doxorubicin 2 mg/kg**
- **Vehicle Controls**

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**Targeted TAP-alkylators:** >40x TI in BRCA mutant ovarian cancer

BRCA1-deficient ovarian cancer PEO1 cells treated at tumor pH are highly sensitive to TAP-targeted DNA-crosslinkers, while the BRCA-repaired sub-strain, PEO4, is both more resistant and less exposed to TAP-therapy at healthy tissue pH. This models a BRCA patient (heterozygous systemically and BRCA-deficient in the tumor).

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**Yale Contact:** David Lewin, Ph.D., Yale University Office of Cooperative Research
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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.

Innovators: Anna Pyle, Ph.D., Akiko Iwasaki, Ph.D.

Yale Contact: John Puziss, Ph.D., Yale University Office of Cooperative Research (203) 785-6167, john.puziss@yale.edu
Using x-ray crystallography, we discovered a previously unknown knob-pocket mechanism critical for intermediate filament (IF) assembly into tetramer building blocks. Mutation of knob residues eliminated tetramer formation.

Vimentin (V) is upregulated in human cancers and is associated with metastasis of cancers. Keratin (K) IFs are upregulated in human cancers and are associated with cancer proliferation. Despite Ks being commonly used in pathology to immunohistochemically identify tumors, there are no anti-cancer drugs currently targeting Ks or other IFs.

Currently, there are no reliable ways to prevent cancer metastasis. We are developing first-in-class anti-cancer treatments by disrupting the K-V IF cytoskeleton.

Our first product will be topical and target Actinic Keratosis (AK) and Squamous Cell Carcinoma (SCC).

**Lead Innovator:** Christopher Bunick, M.D.

**IP Status:** PRV application filed in 2018

Yale Contact: Lolahon Kadiri, Ph.D., Yale University Office of Cooperative Research
(203) 785-4164, lolahon.kadiri@yale.edu
Ovarian tumors with KRAS variant are resistant to treatment with standard chemotherapies including cisplatin.

Yale scientists have discovered that serotonin transport inhibitors selectively inhibit KRAS-variant ovarian cancer.

This method can also be used to specifically treat other cancer, such as breast cancer, with KRAS-variant.

**Intellectual property** patent application pending

Yale Contact: Hong Peng, Ph.D., Yale University Office of Cooperative Research
(203) 785-3074, hong.peng@yale.edu
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).

Inventors: James Hansen, Peter Glazer

IP status: PCT/US2015/047174 filed

References: Weisbart et al., 2015, Sci Rep
Hansen et al., 2012, Sci Transl Med

As shown above, a mouse xenograft model using U87 human glioma cells demonstrate that the cell-penetrating antibody synergizes with doxorubicin in vivo.
**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

**HitProfiling and CYP450s**: clean/excellent metabolic stability

**Biologically Active (b)**: PC3 prostate cancer cells

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**Yale Contact**: David Lewin, Ph.D., Yale University Office of Cooperative Research
(203) 785-6038, david.lewin@yale.edu
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 involving testing piR-37213-L01 in PDX mouse models and uncovering the mechanism of action is under way.

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.

Lead Innovator: Yong Zhu, Ph.D.
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 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.

Yale Contact: Lolahon Kadiri, Ph.D., Yale University Office of Cooperative Research (203) 785-4099, lolahon.kadiri@yale.edu
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.

Figure 1. Anti-GBM effect 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 two (day 0 and day 3) piR-8041 treatments.

Lead Innovator: Yong Zhu, Ph.D.

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

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 colony formation) (Figure 1) and in-vivo (xenograft mouse models in Figure 2). The anti-cancer effect of piR-8041-L01 was highly specific for GBM cancer and had no effect on other cancer types tested (breast, lung, liver, prostate, etc.). Functional analyses suggested that piR-8041 reduces cell proliferation primarily via induction of cell cycle arrest at the G1/S checkpoint, as well as induction of apoptosis.

Figure 2. piR-8041 reduces tumor growth by ~50%. Images of representative mice from each treatment group on day 10 after tumor implantation.
Antigenic peptides help antibody access to the brain

- **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

- **Innovator:** Norifumi Iijima, Akiko Iwasaki


**Yale Contact:** John Puziss, Ph.D., Yale University Office of Cooperative Research (203) 785-6167, john.puziss@yale.edu
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.
- **Innovators:** James Hansen and Jiangbing Zhou
- **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.
Using x-ray crystallography, we discovered a previously unknown knob-pocket mechanism critical for intermediate filament (IF) assembly into tetramer building blocks. Mutation of knob residues eliminated tetramer and IF formation.

Vimentin (V) is upregulated in human cancers and is associated with metastasis of cancers. Keratin (K) IFs are upregulated in human cancers and are associated with cancer proliferation. Despite K being commonly used in pathology to immunohistochemically identify tumors, there are no anti-cancer drugs currently targeting K, V, or other IFs.

Currently, there are no reliable ways to prevent cancer metastasis. We are developing first-in-class anti-cancer treatments by disrupting the K-V IF cytoskeleton.

Our first topical product will target Actinic Keratosis (AK) and Squamous Cell Carcinoma (SCC).

We also working on potential applications in cosmetic dermatology and prevention of scarring/keloids.

- **Lead Innovator:** Christopher Bunick, M.D., Ph.D.
- **IP Status:** PRV application filed in 2018

Yale Contact: Lolahon Kadiri, Ph.D., Yale University Office of Cooperative Research
(203) 785-4164, lolahon.kadiri@yale.edu
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.


Yale Contact: Hong Peng, Ph.D., Yale University Office of Cooperative Research (203) 785-3074, hong.peng@yale.edu
Convection-enhanced Delivery of Drug-Loaded Nanoparticles to the Brain Tumors

- Biodegradable nanoparticles (NPs) have been optimized to penetrate through tumor tissue when delivered by convection-enhanced delivery (CED).
- Delivery of drug-loaded enhanced NPs by CED outperforms treatment with “standard” NPs or drug alone.
- Could also be used to deliver therapeutics to the brain for other indications besides oncology.

References: Zhou et al., 2012 Cancer; 2013 PNAS; Ediriwickrema et al., 2014 Biomaterials; Gaudin et al., 2016 Biomaterials; Saucier-Sawyer et al., 2016 J Control Release.

Patents Applications: 20150118311; 20140371712

Lead Innovator: Mark Saltzman, Ph.D.

Kaplan-Meier survival curves for tumor-bearing rats: blue line, brain-penetrating paclitaxel NPs (median survival 46 d); red line, standard paclitaxel NPs (median survival 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)
Lassa-VSV is a superior safe oncolytic virus for treatment of brain cancers

- Glioblastoma (GBM) are aggressive and invasive brain tumors that generally lead to death within a year of diagnosis.
- No cure exists for this form of cancer and current treatments only prolong life by a few months.
- Lassa-VSV is 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 neurotoxicity that 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:** Anthony van den Pol, PhD

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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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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

OCR 5120: Universal Cancer Vaccine candidate

Immunogenic Epitopes as Targets for Universal Cancer Vaccines

- Unlike other vaccine-based technologies, OCR 5120 is not cancer-type specific, but a “pan-vaccine” antigen opportunity.
- The human immune system can respond to OCR5120 and identify the specific immunogenic epitopes derived from the OCR5120 antigen (see figure) as a matter of surveillance rather than response.

OCR5120 target:
- Is important in self-renewal and maintenance of pluripotency in embryonic stem cells
- Is not cancer-type specific
- Is a “pan-vaccine” antigen

Applications:
- Universal target for a general cancer vaccine
- OCR5120-specific cellular preventive therapy for preventing cancer-like side effects arising from stem cell-based therapies

Published Patent Application

Yale Contact: David Lewin, Ph.D., Yale University Office of Cooperative Research
(203) 785-6038, david.lewin@yale.edu
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 display improved pharmacokinetics and water solubility as compared to previously reported MMP SEPCT probes (i.e. RP805)

**Lead Innovator:** Mehran Sadeghi, PhD

**IP status:** PCT/US2017/026610

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**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).

Yale Contact: Christopher D. Unsworth, Ph.D., Yale University Office of Cooperative Research (203) 785-3846, Christopher.unsworth@yale.edu
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:** 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.
LRRC31 as Master Regulator of DNA Repair  OCR # 7499

- Nonhomologous end-joining (NHEJ) plays a central role in regulation of cancer radiotherapy as well as genome editing
- Dr. Zhou’s lab at Yale identified LRRC31 as a master regulator of the NHEJ machinery
- The Zhou lab demonstrated that targeted upregulation of LRRC31 sensitizes tumors to irradiation and improves the efficiency of CRISPR-mediated precise genome editing
- Intellectual Property: A patent application pending

Yale Contact: Hong Peng, Ph.D., Yale University Office of Cooperative Research (203) 785-3074, hong.peng@yale.edu
Neuroscience and Visual Science
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)

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Mice treated from Day 6 Q3D at 5mg/kg i.p. except for a 10mg/kg dose on Day 9.
Polar Anionic Polymers rescue AD by inhibiting Aβ/PrP

- Amyloid β-oligomers (Aβ) bind to neurons via Prion Protein (PrP), triggering neurotoxic cascade and Alzheimer’s disease
- Polar anionic polymers bind to PrP with high affinity, inhibiting Aβ binding
- Oral delivery of PSCMA (Polymer 3) inhibits the Aβ/PrP interaction and rescues Alzheimer’s Disease-induced learning and memory deficits in mice

Pending Patent: US 62/694710

Innovators:
Stephen M. Strittmatter, M.D., Ph.D.
Erik Christian Gunther, 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 significant behavioral rescue in the setting of advanced disease, even with a relatively short treatment regimen (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.

**Lead Innovator:**
Stephen M. Strittmatter, M.D., Ph.D.

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**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.
Novel small molecule compounds for treating dry AMD

Background: Age-related macular degeneration (AMD) is the leading cause of blindness in elderly patients, affecting more than 8 million individuals in the US alone. Currently, there is no effective therapy for 90% of AMD patients with “dry” or atrophic form of AMD. The retinal pigment epithelial (RPE) cells are vital for proper functioning neurosensory retina. Age-related changes in RPE cells are a hallmark of early AMD and contribute to pathology and visual morbidity associated with advanced AMD.

Invention: Using a HTS assay, we identified a small molecule 424 as the lead compound with IC$_{50}$=~20nM. It is non-toxic in vitro and significantly improves RPE viability in the tert-butyl hydroperoxide (TBHP) challenge assay, which induces oxidative stress (Figure 1).

- Tolerability and pharmacokinetic studies for topical (eye drops) and intravitreal delivery of compound 424 are underway.
- We have identified additional, novel chemotypes that are under development.

IP status: PRV application filed.

Innovators: Mark Fields, Ph.D.,
Lucian Del Priore, M.D., Ph.D.

Figure 1. Treatment with compound 424 significantly enhances human RPE cell viability after challenge with TBHP as measured by luminescence. A. RPE control. B. Compound 424 is non-toxic. C. TBHP induces cell death. D. Compound 424 protects RPE cells from oxidative stress. E. Summary of all experiments
Small molecule drug candidate and delivery system for corneal dystrophy

**Background:** Fuchs’ endothelial corneal dystrophy (FECD) is a progressive, blinding disease characterized by corneal endothelial cell apoptosis. FECD is currently treated only by surgical procedures such as corneal transplant and require extended periods of recovery. Oxidative stress has been demonstrated to play a major role in the pathogenesis of the FECD.

**Inventions:**

(i) Using HTS, we have identified several hit molecules with EC$_{50}$ in the nM range. Our **lead compound** 424 protects corneal endothelial cells from oxidative stress-induced cell death in a dose-dependent manner (Figure A). Med chemistry of 424 is underway.

(ii) We are also developing a novel **non-invasive small molecule ocular drug delivery/formulation system** to optimize delivery and penetration of compound 424. Tolerability and pharmacokinetic studies for topical delivery of the lead compound and the formulation system are underway.

**IP status:** PRV application filed.

**Innovators:** Mark Fields, Ph.D.,

Lucian Del Priore, M.D., Ph.D.

Figure A. Treatment with the compound 424 (not formulated) significantly enhances corneal endothelial cell viability after challenge with TBHP (which induces oxidative stress), as measured by luminescence.
Antigenic peptides help antibody access to the brain

**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

**Innovator:** Norifumi Iijima, Akiko Iwasaki

**Reference:**


Yale Contact: John Puziss, Ph.D., Yale University Office of Cooperative Research (203) 785-6167, john.puziss@yale.edu
Novel endothelial-specific molecules (ESMs) actively cross BBB and carry other molecules with them

- **The Problem:** Brain and retina are shielded to prevent entry of infectious agents and toxins and maintain ionic homeostasis. >98% of small molecules and macromolecules are prevented from crossing the BBB and BRB. Drugs that cross BBB are limited to small lipophilic molecules. Larger hydrophilic molecules do not cross BBB/BRB. We created a library of tens of small molecule ESMs with exquisite specificity and efficiency for entering blood endothelial cells and tested them *in vivo*.

- **Our solution:** ESMs are inherently fluorescent and can be tracked *in vivo* (*Fig1*)
  - ESMs cross BBB through SLC membrane transporters, reach endothelial cytosol and nucleus, when administered topically (*Fig 2*) and I.V. (not shown)

- ESMs *can be conjugated* to molecules up to 1000 Da (testing of large molecules under way) without loss of BBB-crossing properties and endothelial specificity and *serve as molecular trojan hoses to transport drug across the BBB* (*Fig 3*).

- **Lead Innovator:** Jaime Grutzendler, M.D.
- **IP Status:** PRV application filed in 2018

Yale Contact: Lolahun Kadiri, Ph.D., Yale University Office of Cooperative Research
(203) 785-4164, lolahun.kadiri@yale.edu

**Figure 1.** In vivo 2-photon brain imaging set up.

**Figure 2.** Specific vascular labeling by topical application of ESMs to retina (left) and brain surface (right)

**Figure 3.** ESM-Methotrexate Conjugate. *In vivo* two-photon imaging of brain cortex showing endothelial and interstitial labeling with an ESM-methotrexate conjugate.
mGluR5 Silent Allosteric Modulator For Treatment of Alzheimer’s Disease

• **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 allosteric modulator (SAM) has been identified that blocks Ab binding, **but does not interfere with normal glutamate signaling.**

• Treatment of AD mice with SAM improves memory and learning (Fig.1), and ameliorates synaptic loss (Fig.2).

• **IP status:** Extensive patent portfolio covers novel composition of matter and is available for licensing.

• **Lead Innovator:** Stephen M. Strittmatter, M.D., Ph.D.


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.*

Yale Contact: John Puziss, Ph.D., Yale University Office of Cooperative Research (203) 785-6167, john.puziss@yale.edu
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
- Lead Innovator: Zhengxin Cai, PhD
- IP status: Provisional application pending 62/460,541

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.

Yale Contact: Christopher D. Unsworth, Ph.D., Yale University Office of Cooperative Research (203) 785-3846, Christopher.unsworth@yale.edu
Blocking the transforming growth factor-β (TGF-β) pathway in peripheral macrophages can 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 blood-brain barrier to enter the brain.

Expression of a CD11c promoter–driven dominant-negative 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

Yale Contact: Hong Peng, Ph.D., Yale University Office of Cooperative Research (203) 785-3074, hong.peng@yale.edu
OCR 5570: Novel Druggable Target to Treat Bipolar Disease

- 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
- OCR5570 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

Yale Contact: David Lewin, Ph.D., Yale University Office of Cooperative Research
(203) 785-6038, david.lewin@yale.edu
Previous dual-brain studies during social interaction have demonstrated synchronization of brain activity of adult participants.

Characterization of cross-brain synchronization between children and their mothers can be used to understand social communication in ASD using a novel, clinically usable, non-invasive brain imaging technology, functional near-infrared spectroscopy (fNIRS).

It is hypothesized that cross-brain synchronization of regions associated with language, song, and vision occurs in typically developing infants or toddlers and their mothers during communication.

In contrast, we predict that infants and toddlers at high risk for autism will show reduced or altered cross-brain synchronization with their mother’s brain activity during speech or songs.

Although high-risk infants have similar brain patterns to children diagnosed with ASD, they do not show the characteristic ASD behavior. Therefore this may be a novel way to diagnose autism in high-risk infants much earlier than current methods.

**Lead Innovator:** Joy Hirsch, PhD

**IP status:** PCT/US15/58835 pending

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**Yale Contact:** Christopher D. Unsworth, Ph.D.,
Yale University Office of Cooperative Research
(203) 785-3846, Christopher.unsworth@yale.edu
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)

<table>
<thead>
<tr>
<th>Approach</th>
<th>Number of Probes</th>
<th>Reliability</th>
<th>Ease of Use</th>
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Contact: Richard Andersson, MEng, Yale University Office of Cooperative Research
(203) 436-3946, richard.andersson@yale.edu
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.

**Lead Innovator**: Chris Pittenger, MD/PhD

**Yale Contact**: Christopher D. Unsworth, Ph.D., Yale University Office of Cooperative Research  
(203) 785-3846, Christopher.unsworth@yale.edu
Abnormal phosphorylation of tau is a classical hallmark of Alzheimer’s and some other neurodegenerative diseases.

Fine detail analysis of the cellular location of various signaling components in the primate prefrontal cortex (PFC) identified a mechanism whereby phosphorylated tau accumulates with aging.

Based on this hypothesis, chronic treatment (daily for 6 months) with low doses of a known, now generic, therapeutic was shown to enhance cognition and reduce the level of phosphorylated tau in the primate PFC (see figure).

A patent application has been filed on this use of the low dose of this generic compound.
Therapeutics:
Cardiac, Pulmonary, Hepatic, Metabolic and Fibrotic Disease
**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
- **Innovator:** Hyung J. Chun, MD, FAHA

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**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.
(**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. VEGF 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 endothelial-specific) 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.

**Innovator:** Michael Simons, M.D.

**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).
Atherosclerosis is initiated by sub-endothelial accumulation of LDL.

Endothelial cells can take up LDL independent of the LDL Receptor (LDLR).

A GW siRNA library screen identified ALK-1 as a mediator of LDLR-independent LDL uptake.

Loss of ALK-1 leads to reduced endothelial LDL uptake in vivo.

ALK-1 antibodies or decoy proteins are under evaluation as potential therapeutics for atherosclerosis.

A provisional patent application has been filed.


Yale Contact: Christopher D. Unsworth, Ph.D., Yale University Office of Cooperative Research
(203) 785-3846, Christopher.unsworth@yale.edu
Recombinant Protein for Treatment of Coronary Artery Disease (CAD) and Metabolic Syndrome (MetS)

- Genetic analysis of a kindred displaying marked early onset CAD, type 2 diabetes, hypertension and hypertriglyceridemia identified mutations in a specific gene.
- The protein encoded by this gene is ubiquitously expressed and found in the plasma, the mutations result in loss of its enzymatic function.
- In *in vitro* studies the wild-type enzyme increased Insulin release in the presence of high glucose (top figure) while *in vivo* treatment of mice markedly dropped blood glucose levels (lower figure).
- This recombinant protein is a promising candidate for treatment of CAD, MetS and related disorders.
- **IP status**: provisional patent application filed.

*Yale Contact*: Christopher D. Unsworth, Ph.D., Yale University Office of Cooperative Research (203) 785-3846, Christopher.unsworth@yale.edu
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 OCR 7314:

• 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.

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

2. OCR7314 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.
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

Lead Innovator: Michael Simons, M.D.

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-/-
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

**Lead Innovator:** Hyung Chun, MD, FAHA

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**Yale Contact:** John Puziss, Ph.D., Yale University Office of Cooperative Research
(203) 785-6167, john.puziss@yale.edu
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

- **Innovator:** Tarek Fahmy, Ph.D.
- **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.

**Yale Contact:** John Puziss, Ph.D., Yale University Office of Cooperative Research  
(203) 785-6167, john.puziss@yale.edu
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.


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

**Innovator:** Hyung Chun, M.D.

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

Yale Contact: John Puziss, Ph.D., Yale University Office of Cooperative Research (203) 785-6167, john.puziss@yale.edu
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

**Lead Innovator:** Naftali Kaminski, M.D.

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**PARTNERED**

_Yale Contact: John Puziss, Ph.D., Yale University Office of Cooperative Research (203) 785-6167, john.puziss@yale.edu_
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 Sobetirome (GC-1) attenuate hyperoxia induced ALI in WT mice.

**IP Status**: U.S. provisional patent application 62/641,643

**Innovators:**
- Naftali Kaminski, MD
- Patty Lee, MD

**Yale Contact:** John Puziss, Ph.D., Yale University Office of Cooperative Research (203) 785-6167, john.puziss@yale.edu
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

*Yu et al, Nature Medicine 2018*

**IP Status:** PCT/US 15/317,276

**Innovator:** Naftali Kaminski, M.D.

Yale Contact: John Puziss, Ph.D., Yale University Office of Cooperative Research
(203) 785-6167, john.puziss@yale.edu
**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 OCR7575 as a target (D).

**Innovator:** Jonathan Bogan
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” program for 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, co-crystal structures, published biology and pathway understanding, proven team

**Yale Contact**: David A. Lewin, Ph.D., Yale University Office of Cooperative Research (203) 785-6038, david.lewin@yale.edu
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 (B)

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

**Yale Contact**: David A. Lewin, Ph.D., Yale University Office of Cooperative Research (203) 785-6038, david.lewin@yale.edu

**Innovators**: **Lee, Bucala**

**Issued and pending patents**
Therapeutics: Inflammatory and Autoimmune disorders, Immunomodulation
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.
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.


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Yale Contact: Lolahon Kadiri, M.D., Ph.D., Yale University Office of Cooperative Research, (203) 785-6038, Lolahon.kadiri@yale.edu
Inflammasome-mediated inflammatory disease treatment with β-hydroxybutyrate and similar compounds

- NLRP3 inflammasome activation is implicated in a number of diseases such as gout, atherosclerosis, type-2 diabetes, Alzheimer's disease, multiple sclerosis, Muckle-Wells Syndrome (MWS), Familial Cold Autoinflammatory Syndrome (FCAS).

- The ketone body β-hydroxybutyrate (BHB) as well as γ-hydroxybutyric acid (GHB) can inhibit NLRP3 inflammasome activation. BHB delivery in vivo reduced NLRP3 inflammasome-mediated Interleukin (IL)-1β secretion, reversing phenotypes in animal models with gout, MWS, FCAS, and peritonitis.

- **Intellectual property** – US patent application pending


Reduction of neutrophil infiltration as well as NLPR3 inflammasome and related cytokines in the ketogenic diet fed mouse model.

**Yale Contact**: Hong Peng, Ph.D., Yale University Office of Cooperative Research
(203) 785-3074, hong.peng@yale.edu
**Structure-based design of MIF Antagonists**

(a) Structure-based design with validated target

![Structure diagram showing key residues and interactions](image1)

**Novel/Improved Assays for SAR**

![Assay graph showing binding curves](image2)

**Potent/Drug-like Leads**

- OCR6558-316, Kd = 0.181 μM
- OCR6558-334, Kd = 0.056 μM

**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

**HitProfiling and CYP450s**: clean/excellent metabolic stability

**Biologically Active (b)**: PC3 prostate cancer cells

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Yale Contact: David Lewin, Ph.D., Yale University Office of Cooperative Research
(203) 785-6038, david.lewin@yale.edu
MIF-2 (aka D-DT) has utility for the prevention and repair of ischemia/reperfusion AKI.

Validity of Human Clinical Hypothesis: Genetically characterized 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).

Innovators: Bucala, Young, Moeckel

IP: Issued & Pending Patents

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Yale Contact: David A. Lewin, Ph.D., Yale University Office of Cooperative Research (203) 785-6038, david.lewin@yale.edu
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)
- 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
Vaccines & Infectious Disease
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
**OCR6245: In vivo Long-term CR NNRTI**

**Long-acting CR-NNRTIs to Treat HIV**

- Marked synergy with current FDA-approved NRTIs (e.g. tenofovir (TDF), INSTIs, and pharma clinical compounds) (A)
  - Excellent candidate for combination therapy regimens
  - Pre-Exposure Prophylaxis (PrEP)

- Highly soluble with 2-21 nM potency vs. drug-resistant strains, including K101P (e.g., rilpivirine ineffective against K101P) in MT-2 T-cell/HIV-1 assay

- Excellent ADME-Tox and physiological properties (B)
  - No off targets including HERG and CYP3A
  - Excellent in vivo oral bioavailability in mice

- Efficacy in humanized mouse AIDS model (C)
  - CD4+; viral load undetectable
  - Single dose, long-acting (4 week) sustained release nanoparticle formulation

- Issued US Patent 9,382,245 and related pending IP & Publications

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Yale Contact: David Lewin, Ph.D., Yale University Office of Cooperative Research
(203) 785-6038, david.lewin@yale.edu
Novel cell wall synthesis inhibitors with appended siderophores have:

- Improved penetration into and growth inhibition of Gr- bacteria
- Decreased susceptibility beta-lactamases; avoiding a major cause of resistance
- Expanded spectrum of inhibition
- Concise modular synthesis
- Do not contain a beta-lactam ring, decreasing likelihood of allergic response
- **Superior potency vs clinical isolates when compared to ceftazidime, imipenem, etc.**
- **IP status:** PCT/US2019/042643
- **Lead Innovator:** Mark Plummer, PhD

Yale Contact: John Puziss, Ph.D., Yale University Office of Cooperative Research
(203) 785-6167, john.puziss@yale.edu
OCR6913: Whole cell vaccine/adjuvant platform

- Effective vaccines against many bacteria require T cell immunity, but few vaccines elicit such responses.
- OCR6913 is a chemical technique for attaching a T cell-stimulating adjuvant (CPX2) directly to bacteria.
- This adjuvant potently activates T cell-promoting signals through TLR7.
- Demonstrated protective effect of the vaccine in vivo in S. aureus bacteremia.
- This chemistry allows synthesis of whole cell vaccines against any culturable bacteria or fungus.

Yale Contact: David Lewin, Ph.D., Yale University Office of Cooperative Research
(203) 785-6038, david.lewin@yale.edu
OCR7106: Novel Pleuromutilin Antibiotics

Total Synthesis and Synthetic Route for Novel Antibiotics

- **About the Pleuromutilins**
  - Bacterial protein synthesis inhibitor
  - Pleuromutilins approved/in the clinic
    - Approved (retapalmulin; Altabax®) for topical use (impetigo)
    - Phase 3: lefamulin (oral) various bacterial indications

- **Current production Pleuromutilins**
  - >3000 semisynthetic derivatives prepared modulated at C14
  - Little other exploration due to synthetic difficulties

- **Future Production/Novel Pleuromutilins**
  - Total synthesis at high efficiency
    - Commercially viable routes; high overall yield, short convergent synthesis
    - Ability to modulate ring size, introduce atomic substitutions, conduct deep SAR
  - Complete stereocontrol
  - Total synthesis facilitates novel chemistry

- **OCR7106 IP Status:**
  - Publications (Science, etc.)
  - Multiple patents filed (available under CDA)

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**Prior syntheses:**
- Gibbons, 1982
  - 31 linear steps racemic
- Boeckmann, 1989
  - 27 linear steps racemic
- Procter, 2013
  - 34 linear steps enantioselective

**New Synthesis**
- tricyclic core
- 8-membered ring
- 8-contiguous stereocenters
- 3 quaternary centers

**Ten steps to entire skeleton**

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Yale Contact: David Lewin, Ph.D., Yale University Office of Cooperative Research
(203) 785-6038, david.lewin@yale.edu
Leptospira is a major veterinary pathogen and can cause a life-threatening disease in humans.

Current vaccines provide limited protective value.

Yale researchers have generated a live, attenuated strain of Leptospira that provides protective immunity.

Vaccination with this strain protects against a lethal challenge with various Leptospira species.

OCR6320 is a safe and efficacious novel vaccine candidate for the treatment of Leptospira infections.


Partnered for vet use; Human use still available.


Lead Innovator: Albert Ko, M.D.
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, OCR 6185 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

**Lead Innovator:** Jorge Galan, PhD, DV

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**Yale Contact:** John Puziss, Ph.D., Yale University Office of Cooperative Research
(203) 785-6167, john.puziss@yale.edu
• Malaria is a worldwide infectious disease, causing over 1M deaths annually. RTS,S (Mosquirix™), the world’s only licensed malaria vaccine targets the circumsporozoite protein (CSP) and is only 27-46% effective.

• A novel vaccine approach targets mosquito saliva components. Mosquito saliva is injected into patients along with malaria parasite.

• Immunizing mice with antibodies against SG1L3, the lead mosquito salivary protein, showed substantial reduction of Plasmodium liver burden and parasitemia, when challenged with infected mosquito.

• Intellectual property – A provisional patent application has been filed


Effects of immunizing mice with SG1L3 antibodies (A) Plasmodium liver burden in mice with no treatment, a known Plasmodium sporozoite transmission inhibitor (3D11 mAb against P. berghei CSP), an SG1L3 antibody, and an SG1L3 antibody and 3D11 mAb combination; (B) effect of SG1L3 antibodies on parasitemia in mice.
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 RT inhibitors (NNRTIs) that address continuing issues:
- concerning the possible emergence of new viral strains
- improved dosing
- long-term tolerability
- safety

OCR5753 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 EC\textsubscript{50} of 55 picomolar.

OCR5753 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.

Patent Application & Reference

Yale Contact: David Lewin, Ph.D., Yale University Office of Cooperative Research
(203) 785-6038, david.lewin@yale.edu
Treatment of HIV infection by inhibiting Toll-like receptor 7 signaling

- Existing anti-viral drugs focus on suppressing viral activity rather than awakening the host’s immune system;

- Activation of the Toll-like receptor 7 (TLR7) on CD4+ T cells results in down-regulation of immune response known as T-cell anergy;

- Inhibitors of TLR7 reverse T-cell anergy caused by HIV infection, as well as reduce HIV activity in both in vitro and ex vivo systems made of cells from HIV patients;

- In vivo study using a humanized mouse model confirms the efficacy of TLR7 blockade in treating HIV infection; and

- This mechanism should open up a new avenue in the fight against HIV.

**Lead Innovator:** David Hafler, M.D.


Yale Contact: Hong Peng, Ph.D., Yale University Office of Cooperative Research (203) 785-3074, hong.peng@yale.edu
• **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 multi-drug 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

• **Lead Innovator**: Paul Turner, Ph.D.

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**Yale Contact:** John Puziss, Ph.D., Yale University Office of Cooperative Research
(203) 785-6167, john.puziss@yale.edu
Tick Antifreeze Glycoprotein to Treat Antibiotic-Resistant Bacterial Infection

- Bacterial biofilm formation on indwelling devices is one of the mechanisms that cause antibiotic drug-resistance and bears annual healthcare burden $1 bn in the US.
- As bacteria dispersed from a biofilm usually rapidly become susceptible to antibiotics, drugs against biofilm formation provide an alternative opportunity to combat infectious diseases.
- A tick antifreeze glycoprotein IAFGP, and a derived synthetic peptide P1 function as an anti-virulence agent against diverse bacterial species by disrupting formation of biofilm.
- IAFGP and P1 can be used as potent anti-microbial agent, alone or in combination with other antibiotics such as Ciprofloxacin and Daptomycin.

- **Intellectual property** – PCT patent application has been filed (Publication WO 2015/095349)
- **Reference:** Heisig, Martin et al. (2014) Cell Report

Yale Contact: Lolahon Kadiri, Ph.D., Yale University Office of Cooperative Research (203) 785-4164, lolahon.kadiri@yale.edu
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 Pending

![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.](image-url)
A novel, effective anti-bacterial peptide-morpholino oligomer

- Novel composition combining novel cell penetrating peptide (CPP) with morpholino oligomer
- The conjugate transports morpholino oligomer sequence into bacteria with 10-100 fold more efficiency than previous known peptides
- The conjugate has a broad range of potency against pathogenic bacteria
- Patent: U.S. patent issued No. 9,801,948

Table 1: Loss of viability of bacterial phenotype (containing drug resistant genes) when mixed with CPP-PMO conjugate

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>Conjugate</th>
<th>Conc., μM</th>
<th>Viability</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>AB1-CAT</td>
<td>0.5</td>
<td>10^{-6}</td>
</tr>
<tr>
<td>S. typhimurium</td>
<td>gyr313-14</td>
<td>0.5</td>
<td>10^{-3}</td>
</tr>
<tr>
<td>B. subtilis</td>
<td>gyr313-14</td>
<td>0.5</td>
<td>6x10^{-6}</td>
</tr>
<tr>
<td>P. syringae</td>
<td>gyr313-14</td>
<td>2</td>
<td>6x10^{-2}</td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>gyr313-11</td>
<td>0.5</td>
<td>3x10^{-3}</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>gyr313-14</td>
<td>0.5</td>
<td>4x10^{-5}</td>
</tr>
<tr>
<td>S. aureus</td>
<td>Sagyr313-14</td>
<td>5</td>
<td>7.5x10^{-4}</td>
</tr>
<tr>
<td>Enterobacter</td>
<td>AB1-CAT</td>
<td>5</td>
<td>0.02</td>
</tr>
<tr>
<td>Enterobacter</td>
<td>AB2-gyr313-11</td>
<td>5</td>
<td>0.08</td>
</tr>
<tr>
<td>S. aureus</td>
<td>AB2-gyr313-14</td>
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<td>0.30</td>
</tr>
<tr>
<td>E. faecalis</td>
<td>AB2-gyr313-11</td>
<td>2</td>
<td>0.03</td>
</tr>
<tr>
<td>M. marinus</td>
<td>AB1-mmbla</td>
<td>1</td>
<td>0.27</td>
</tr>
<tr>
<td>M. marinus</td>
<td>AB1-gyr313</td>
<td>1</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Contact: Hong Peng, Ph.D., Yale Office of Cooperative Research (203) 785-3074, hong.peng@yale.edu
Dr. Andrew Goodman’s research shows that the gut microbes were responsible for producing 20-80% of the circulating toxic metabolites derived from 3 drugs.

Combining gut commensal genetics with gnotobiotics, they measured brivudine drug metabolism across tissues in mice that vary in a single microbiome-encoded enzyme.

Built a pharmacokinetic model that quantitatively predicts microbiome contributions to systemic drug and metabolite exposure, as a function of bioavailability, host and microbial drug-metabolizing activity, drug and metabolite absorption, and intestinal transit kinetics.

• 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

**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.
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.

**Intellectual Property**: Patent application pending.

**Reference**: Cobalt (III)-Catalyzed C-H Amidation of Dehydroalanine for the Site-Selective Structural Diversification of Thiostrepton.


<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>MIC (ug/ml)</th>
<th>SOLUBILITY (ug/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Staph. Aureus MSSA</td>
<td>Staph. Aureus MRSA</td>
</tr>
<tr>
<td>Thiostrepton</td>
<td>0.06</td>
<td>0.12</td>
</tr>
<tr>
<td>Analogs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RJS-01</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>RJS-04</td>
<td>0.5</td>
<td>0.5</td>
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</tr>
<tr>
<td>RJS-10</td>
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<tr>
<td>RJS-12</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>RJS-15</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>RJS-16</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>
Cellular Therapy, Regeneration & Wound-healing
A Biomimetic System that Replicates how T-Cells are Expanded in the body

A T-cell expansion method that uses clusters of carbon nanotubes (CNP) to group stimuli together and expand T-cells.

Advantages

- 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*
- And consistently higher than the gold standard Dyna beads – *top figure*
- CNPs are continuously better at T-cell expansion than other methods *in vivo* – *bottom figure*
- Uses 1 ng of reagents for 1 million cells
- Use 1000x less of T-cell growth factor IL-2

Yale Contact: Richard Andersson, Yale University Office of Cooperative Research  
(203) 436-3946, richard.andersson@yale.edu
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

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

**Yale Contact**: Hong Peng, Ph.D., Yale University Office of Cooperative Research  
(203) 785-3074, hong.peng@yale.edu
Yale scientists have developed novel methods of increasing pluripotency of stem cells. The methods include contacting stem cells with Rho-associated kinase inhibitor and Arp2/3 complex inhibitor, which together increase the pluripotency of stem cells in a surprising and synergistic manner.

These methods can be useful for treatment of cancer, fibrosis, and/or inflammation.


Intellectual property – patent application pending

Yale Contact: Hong Peng, Ph.D., Yale University Office of Cooperative Research
(203) 785-3074, hong.peng@yale.edu
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 conventional CD8α or CD28 transmembrane domain.

**Yale Contact:** Hong Peng, Ph.D., Yale University Office of Cooperative Research (203) 785-3074, hong.peng@yale.edu
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.

Yale researchers have identified 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

Patent Application & Reference

Yale Contact: Lolahon Kadiri, Ph.D., Yale University Office of Cooperative Research (203) 785-4164, lolahon.kadiri@yale.edu
Planar retinoid solves problems with current technology:

- Human model that emulates the choroid, retinal pigment epithelium (RPE), neurosensory retina, and vitreous in their native anatomical relationship.
- Scaffold and co-culture with RPE generates laminated retinoids for implantation 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.
- Provisional patents filed
Inadequate blood vessel formation is a major contributor to poor wound healing particularly with diabetic ulcers.

Yale researchers have discovered that a unique domain from a known protein can promote VEGF signaling by associating with the VEGFR.

Injecting this 27 amino acid peptide (SP) i.p. in neonatal mice increased retinal vessel growth.

Topical application of the peptide to the injury site in mice after ear punch markedly enhanced the rate of wound healing.

A provisional patent application has been filed.
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 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.

**Lead Innovator:** Christopher Bunick, M.D., Ph.D.

**IP Status:** PRV application filed in 2018

Yale Contact: Lolahon Kadiri, Ph.D., Yale University Office of Cooperative Research (203) 785-4164, lolahon.kadiri@yale.edu
Immunoevasive human endothelial cells (ECs) have been developed using CRISPR/Cas9 gene editing technology to knock out the genes (CIITA, a class II major histocompatibility complex transactivator, and CD58) eliminating ECs’ immunogenicity.

These immunoevasive cells retain the capacity to self-assemble into vascular structures in vivo and can be readily cultured from cord blood.

Therefore these cells offer great potential for tissue repair or graft perfusion without eliciting immunorejection.

**Intellectual property:** US patent application pending


**Stage of Development:** Proof of principle in vivo studies are under development.
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 and differentiation
  - drug screening platform for cell proliferation, differentiation, and regeneration
  - Produce proteins by transfection or transduction of DNA or 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 unlimited source of cells for therapy

Patent Application & Reference

Yale Contact: David Lewin, Ph.D., Yale University Office of Cooperative Research
(203) 785-6038, david.lewin@yale.edu
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 LOF mutation leads to ichthyosis vulgaris, the most common disorder of keratinization, and a strong genetic risk factor for atopic eczema.

- 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, post-keratin binding and have limited efficacy.

- We have identified two specific short (60-150 a.a.) segments of FLG that are critical for keratin aggregation. We are developing novel peptide-based agents that promote FLG-K binding; these can serve as novel treatment for atopical dermatitis, ichthyosis, psoriasis, and other skin conditions, as well as basis for new type of skin moisturizers.

- **Lead Innovator:** Christopher Bunick, M.D.

- **IP Status:** PRV application filed in 2018
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.

**Over-expression of the genes extends lifespan and stress-resistance 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.


Gene Therapy & Genome Engineering
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
- Lead Innovator: W. Mark Saltzman, Ph.D.
- 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.
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;
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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.

Yale Contact: John Puziss, Ph.D., Yale University Office of Cooperative Research (203) 785-6167, john.puziss@yale.edu
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

**Lead Innovator:** Peter Glazer, Ph.D.

**IP status:** pending "COMPOSITIONS AND METHODS FOR ENHANCING DONOR OLIGONUCLEOTIDE-BASED GENE EDITING"
Precise engineering of protein materials and biologics

• Enable manufacturing of genetically encoded materials (GEMs) for applications in medicine, electronics, environmental sustainability, fabrics, aerospace, and beyond
• Established broad proprietary platform for programmable 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 delivery and vaccines
  • Preliminary in vivo data demonstrates lack of immunogenicity to synthetic amino acids used in GEMs

How it works:

1. Express biologic in Pearl Platform
2. Extract and react to functionalize
3. Characterize

Team: Farren Isaacs, PhD, Michael Jewett, PhD, Natalie Ma, PhD, Barry Schweitzer, PhD


Yale Contact: David Lewin, Ph.D., Yale University Office of Cooperative Research
(203) 785-6038, david.lewin@yale.edu
Site-Specific Efficient Incorporation of Phosphoserine into Proteins Using a Novel EF-Tu and tRNA Charging System

- In general, phosphoproteins are highly unstable and difficult to produce.
- OCR3105/5254 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 technology provides a method of site specific cotranslational incorporation of phosphoserine into proteins, including human MEK-1.
- The production of phosphoprotein is inducible by phosphoserine and the system is compatible with transgenic methodologies.
- Applications:
  - research tools for the study of 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

Yale Contact: David Lewin, Ph.D., Yale University Office of Cooperative Research
(203) 785-6038, david.lewin@yale.edu
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”

Yale Contact: David Lewin, Ph.D., Yale University Office of Cooperative Research
(203) 785-6038, david.lewin@yale.edu
Orphan & Rare Diseases
Wolfram syndrome = rare genetic disorder
- Loss of function of gene WFS1
- Homozygous mutation (1 in 770,000 in US)
  - blindness, deafness, mood disorders
- Heterozygous patients
  - 1% of US, 8-fold higher mood disorders
- No available treatment
  - palliative care only
- Target structures + hits known
- Screenable/Structure-based drug design
- Animal models available for in vivo validation

Yale Contact: David Lewin, Ph.D., Yale University Office of Cooperative Research
(203) 785-6038, david.lewin@yale.edu
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

Current Periodontal Surgery Reimbursement:
- Detail
- Detail
- Detail

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®

Yale Contact: David A. Lewin, Ph.D., Yale University Office of Cooperative Research (203) 785-6038, david.lewin@yale.edu
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).


**Intellectual Property:** US patent issued No. 10,357,549

Yale Contact: Hong Peng, Ph.D., Yale University Office of Cooperative Research
(203) 785-3074, hong.peng@yale.edu
OCR 5775 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 the absence of OCR 5775 (blue curve) in a patient with a poorly characterized platelet storage disease. The addition of 50 nanomolar of OCR5775 (black curve) normalizes the clotting profile.

This technology may also have utility in a critical care situation such as the Emergency Department for acute bleeding episodes (e.g., NSAID toxicity), first response, or military situations.

Yale Contact: David Lewin, Ph.D., Yale University Office of Cooperative Research (203) 785-6038, david.lewin@yale.edu

Patent Application & Reference
Drug delivery: Nanoparticles, Topical Technology & Sustained Delivery
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
- **Lead Innovator**: W. Mark Saltzman, Ph.D.
- **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.

**Yale Contact**: John Puziss, Ph.D., Yale University Office of Cooperative Research  
(203) 785-6167, john.puziss@yale.edu
Antigenic peptides help antibody access to the brain

**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

**Innovator:** Norifumi Iijima, Akiko Iwasaki

**Reference:**

Yale Contact: John Puziss, Ph.D., Yale University Office of Cooperative Research (203) 785-6167, john.puziss@yale.edu
3E10 is a **cell-penetrating** mAb that **transports** DNA/RNA into cells and tissues in vivo

- **Therapeutic applications:**
  - Delivery of gene therapy constructs (e.g. CAR T cells, cure of orphan genetic diseases)
  - Delivery of therapeutic mRNAs
  - Delivery of therapeutic antisense oligos
  - Delivery of siRNAs
  - Delivery of oligos for gene editing to correct mutations causing genetic disorders

- **Advantages:**
  - No need for nuclease
  - Established manufacturing processes for both components
  - The approach has no sequence limitations to reagent design
  - Reduced off-target activity

- **Lead Innovator:** Peter Glazer, MD PhD
- **IP status:** Provisional patent application filed

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**Yale Contact:** John Puziss, Ph.D., Yale University Office of Cooperative Research  
(203) 785-6167, john.puziss@yale.edu
Novel endothelial-specific molecules (ESMs) actively cross BBB and carry other molecules with them

- **The Problem:** Brain and retina are shielded to prevent entry of infectious agents and toxins and maintain ionic homeostasis. >98% of small molecules and macromolecules are prevented from crossing the BBB and BRB. Drugs that cross BBB are limited to small lipophilic molecules. Larger hydrophilic molecules do not cross BBB/BRB. We created a library of tens of small molecule ESMs with exquisite specificity and efficiency for entering blood endothelial cells and tested them *in vivo*.

- **Our solution:** ESMs are inherently fluorescent and can be tracked *in vivo* (*Fig1*)
- ESMs cross BBB through SLC membrane transporters, reach endothelial cytosol and nucleus, when administered topically (*Fig 2*) and I.V. (not shown)

- ESMs *can be conjugated* to molecules up to 1000 Da (testing of large molecules under way) without loss of BBB-crossing properties and endothelial specificity and *serve as molecular trojan hoses to transport drug across the BBB* (*Fig 3*).

- **Lead Innovator:** Jaime Grutzendler, M.D.
- **IP Status:** PRV application filed in 2018

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**Yale Contact:** Lolahon Kadiri, Ph.D., Yale University Office of Cooperative Research
(203) 785-4164, lolahon.kadiri@yale.edu
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
- **Innovator:** Tarek Fahmy, Ph.D.
- **IP status:** PCT/US Application filed 62/214,648
- **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.

Yale Contact: John Puziss, Ph.D., Yale University Office of Cooperative Research
(203) 785-6167, john.puziss@yale.edu
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)
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
- IP status: pending applications: US15/573,807, EP16727876.1, HK18112243
- Lead Innovator: Mark Saltzman, Ph.D.

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
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.
Diagnostics/Biomarkers/Imaging
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.

A PCT patent application has been filed.

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.

Yale Contact: Christopher D. Unsworth, Ph.D., Yale University Office of Cooperative Research
(203) 785-3846, Christopher.unsworth@yale.edu
Detection of β cell death in diabetes using differentially methylated circulating DNA

- A powerful biomarker and diagnostic indicators have been identified for ongoing β cell death in diabetic patient;
- A method of measure such marker has been developed


Intellectual Property: US and European patents are issued

Contact: Hong Peng, Ph.D., Yale University; (203) 785-3074, hong.peng@yale.edu
NOVEL DEUTERIUM METABOLIC IMAGING (DMI)

- 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 2H-glucose 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: PRV filed.
- Innovators: Henk De-Feyter, Robin de Graaf.

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 cerebrospinal fluid from the left lateral ventricle. e) 3D illustration of combined MRI and DMI of the lactate/Glx ratio representing the spatial distribution of the Warburg effect.
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 patent application has been filed.

Yale Contact: Christopher D. Unsworth, Ph.D., Yale University Office of Cooperative Research (203) 785-3846, Christopher.unsworth@yale.edu
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- **Lead Innovator:** Jaime Grutzendler, M.D.
- **IP Status:** PRV application filed in 2018

**Figure 1.** In vivo 2-photon brain imaging set up.

**Figure 2.** Specific vascular labeling by topical application of ESMs to retina (left) and brain surface (right)

**Figure 3.** ESM-Methotrexate Conjugate. *In vivo* two-photon imaging of brain cortex showing endothelial and interstitial labeling with an ESM-methotrexate conjugate.
Functional near infrared spectroscopy (fNIRS) as a diagnostic tool for Autism Spectrum Disorder (ASD) in high risk infants and toddlers

- Previous dual-brain studies during social interaction have demonstrated synchronization of brain activity of adult participants.
- Characterization of cross-brain synchronization between children and their mothers can be used to understand social communication in ASD using a novel, clinically usable, non-invasive brain imaging technology, functional near-infrared spectroscopy (fNIRS).
- It is hypothesized that cross-brain synchronization of regions associated with language, song, and vision occurs in typically developing infants or toddlers and their mothers during communication.
- In contrast, we predict that infants and toddlers at high risk for autism will show reduced or altered cross-brain synchronization with their mother’s brain activity during speech or songs.
- Although high-risk infants have similar brain patterns to children diagnosed with ASD, they do not show the characteristic ASD behavior. Therefore this may be a novel way to diagnose autism in high-risk infants much earlier than current methods.

**Lead Innovator:** Joy Hirsch, PhD

**IP status:** PCT/US15/58835 pending

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Yale Contact: Christopher D. Unsworth, Ph.D.,
Yale University Office of Cooperative Research
(203) 785-3846, Christopher.unsworth@yale.edu
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 display improved pharmacokinetics and water solubility as compared to previously reported MMP SEPCT probes (i.e. RP805)
- **Lead Innovator:** Mehran Sadeghi, PhD
- **IP status:** PCT/US2017/026610

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).

Yale Contact: Christopher D. Unsworth, Ph.D., Yale University Office of Cooperative Research (203) 785-3846, Christopher.unsworth@yale.edu
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 antibiotherapy 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.
- OCR5151 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.

Issued Patent & Reference

Yale Contact: Chris Unsworth, Ph.D., Yale University Office of Cooperative Research (203) 785-3846, christopher.unsworth@yale.edu
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

Lead Innovator: Zhengxin Cai, PhD

IP status: Provisional application pending 62/460,541

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

(Lef) 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

Yale Contact: Christopher D. Unsworth, Ph.D., Yale University Office of Cooperative Research (203) 785-3846, Christopher.unsworth@yale.edu
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

**Lead Innovators:** Dana Peters, Ph.D.; Chenxi Hu, Ph.D.

**Reference:** unpublished work

**Yale Contact:** Lolahon Kadiri, Ph.D., Yale University Office of Cooperative Research (203) 785-4164, lolahon.kadiri@yale.edu
Devices, Methods, Models, & Assays
Metal stent is widely used to restore blood flow in stenotic vessels. In-stent restenosis caused by smooth muscle cell (SMC) proliferation and endothelial denudation are the major drawbacks.

Dr. Laura Niklason designed a novel drug-eluting stent that overcomes the disadvantages.

The novel stent elutes a combination of agents that trigger apoptosis and growth arrest only in SMCs that are in proximity of the stent.

This invention inhibits SMCs locally and selectively, thereby prevent intimal hyperplasia and in-stent restenosis without damaging ECs.

**Intellectual Property:** Patent Application Pending

Yale Contact: Hong Peng, Ph.D., Yale University Office of Cooperative Research
(203) 785-3074, hong.peng@yale.edu
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.

International 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.

Yale Contact: Richard Andersson, Yale University Office of Cooperative Research
(203) 436-3946, richard.andersson@yale.edu
Our solution: a first in class fully functional robust and inexpensive device that can be easily integrated into any cell injection system on the market, manual or robotic. This device provides real time (within 10 ms) confirmation of cell penetration by measuring membrane resistance and is independent of visualization or pressure feedback. We have built a prototype and tested the device on 78 samples.

Potential Applications:
(a) Sperm injection into an egg in human and animal reproduction (i.e., ICSI)
(b) Injection of genetic material, proteins, or other substances into live cells:
   (i) commercial production of drugs, antibodies, and vaccines
   (ii) treatment: cell and gene therapy; cancer therapy
   (iii) research

Intellectual property: A provisional US patent application was filed in October 2018
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:** Provisional Patent Application No. 62/478,341

**Innovators:** James Yu, M.D.; Amandeep Mahal
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.


**Intellectual Property:** Patent Application Pending

Yale Contact: Hong Peng, Ph.D., Yale University Office of Cooperative Research
(203) 785-3074, hong.peng@yale.edu
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 into cytidine analogs which leads to U-C mutations and marks new transcripts upon sequencing.
- Broadly applicable to any application with metabolic labeling.

Yale Contact: Lolahon Kadiri, Ph.D., Yale University Office of Cooperative Research (203) 785-4164, lolahon.kadiri@yale.edu
**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)
    - Doppler Ultrasound (E)
  - Cerebral Metabolism (F)
  - Neurotransmission restoration

**Potential Uses**
- Ex vivo drug testing (PK/PD, BBB, ADME-T)
- Ex vivo surgical procedures
- Transplant organ preservation, reclamation, and assessment

**Innovators:** [Sestan Lab](#)

**Pending Patents and Publication**

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**Yale Contact:** David A. Lewin, Ph.D., Yale University Office of Cooperative Research  
(203) 785-6038, david.lewin@yale.edu
A novel enzymatic and fluorescent probe, named ddRlucFcγ [deglycosylation-dependent Renilla luciferase (ddRluc) coupled with the Fc region of human IgG1], to quantify the efficiency of protein’s cytosolic access from outside the cell.

ddRluc contains an asparagine at position 290 to which the N-linked glycan is added, and a threonine at position 292 to ensure glycosylation when the protein is expressed in eukaryotic cells. Linking ddRluc to the Fcγ fragment allows for stability and easy purification of the probe.

A version lacking the N-glycan naturally present in the Fc region, the removal of which eliminates binding to Fc receptors, is also available.

Intellectual property – Experiment protocols, materials and know-hows.

Fig 1. ddRlucFcγ activity is deglycosylation dependent. Total extract from HEK293T cells expressing ddRlucFcγ (top) and purified ddRlucFcγ isolated from transfected human Expi293 cells (bottom) were incubated with or without PNGase F followed by luciferase assay.
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.

**Lead Innovator:** Chris Pittenger, MD/PhD

**Yale Contact:** Christopher D. Unsworth, Ph.D., Yale University Office of Cooperative Research (203) 785-3846, Christopher.unsworth@yale.edu
Previous dual-brain studies during social interaction have demonstrated synchronization of brain activity of adult participants.

Characterization of cross-brain synchronization between children and their mothers can be used to understand social communication in ASD using a novel, clinically usable, non-invasive brain imaging technology, functional near-infrared spectroscopy (fNIRS).

It is hypothesized that cross-brain synchronization of regions associated with language, song, and vision occurs in typically developing infants or toddlers and their mothers during communication.

In contrast, we predict that infants and toddlers at high risk for autism will show reduced or altered cross-brain synchronization with their mother’s brain activity during speech or songs.

Although high-risk infants have similar brain patterns to children diagnosed with ASD, they do not show the characteristic ASD behavior. Therefore this may be a novel way to diagnose autism in high-risk infants much earlier than current methods.

**Lead Innovator:** Joy Hirsch, PhD

**IP status:** PCT/US15/58835 pending

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**fNIRS apparatus for the simultaneous recording of brain activity of mother and child**

**fNIRS detects interaction-induced neural synchrony between mother and “typical developing child”**

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**Diagram:**

- Audio-visual recording
- Mother with Adult NIRS cap
- Baby with Infant NIRS cap
- fNIRS system
- Data server for processing and storage

**Graph:**

- Correlation Coefficient
- Mother
- Child
- Integration time span
- Time (seconds)

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**Table:**

- Time (seconds)
- Rel. fNIRs magnitude
- Integration time span
- fNIRS detects interaction-induced neural synchrony between mother and “typical developing child”
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.

Fig 1. 2018 fully-functional HHFNC system prototype with consistent bench level functionality and desired airflow rate of 0-10 L/min, temperature of 32 degrees Celsius and relative humidity of 90-95%.

Contact: Richard Andersson, MEng, Yale University Office of Cooperative Research
(203) 436-3946, richard.andersson@yale.edu
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”.
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- **IP status:** Provisional Patent Application No. 62/481,361
- **Lead Innovators:** Dana Peters, Ph.D.; Chenxi Hu, Ph.D.
- **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
In-vitro lung on a chip system used to test pharmacological intervention of fibrotic diseases. Allows evaluation of matrix composition and stiffness driven fibrotic progression, and reversal using therapeutic intervention.

- First group to decellularize, solubilize, and conjugate matrix from healthy and diseased patient tissues to the tunable hydrogels
- Accurately mimics the tissue microenvironment, i.e., what the cells in the tissue actually sense
- Can very accurately reflect both the healthy and the diseased condition
- Large range of healthy or diseased tissues: lung fibrosis, cirrhosis, heart fibrosis, scleroderma, COPD, emphysema.
- **Innovator**: Anjelica Gonzalez, Ph.D.

The model can reproduce all stages of a disease from healthy to strongly fibrotic by modifying the stiffness of the substrate

**Yale Contact:** Richard Andersson, Yale University Office of Cooperative Research  
(203) 436-3946, richard.andersson@yale.edu
A bioreactor system for whole rat lungs that controls dissolved gas levels (Fig. 1A-B). The system is able to quantify and predict the gas exchange within the bioreactor using a lumped parameter model (Fig. 1C, 2A-B).

This system enables the maintenance of alveolar levels (100 mmHg) of dissolved oxygen for the duration of lung culture.

The mathematical model enables non-invasive and real-time estimation of cell number and the proliferative state of lung tissue simply through dissolved oxygen measurements.

Figure 1 - Design of the whole lung bioreactor for controlling gas exchange.
$C_o$: concentration of oxygen leaving the oxygenator element.
$C_l$: concentration of oxygen leaving the lung.
$F_p$: concentration of oxygen flow out of the bioreactor.
$F_o$: fluid flow rate through the perfusion loop.
$F_t$: fluid flow rate through the oxygenation loop.

Figure 2 – Gas Exchange Characterization Results.

Yale Contact: Hong Peng, Ph.D., Yale Office of Cooperative Research
(203) 785-3074, hong.peng@yale.edu

Patent: US application pending

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.

Contact: Richard Andersson, MEng, Yale University Office of Cooperative Research
(203) 436-3946, richard.andersson@yale.edu
**Portable Compact High Flow Nasal Cannula (HHFNC) Therapy for Neonates and Infants**

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**Contact:** Richard Andersson, MEng, Yale University Office of Cooperative Research (203) 436-3946, richard.andersson@yale.edu
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.

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.

Contact: Richard Andersson, MEng, Yale University Office of Cooperative Research (203) 436-3946, richard.andersson@yale.edu
Biomimetic Lymph node

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

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

**Yale Contact:** Richard Andersson., Yale Office of Cooperative Research
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US Patents 9,737,593; 8,629,098
‘Compositions and methods for adoptive and active immunotherapy’
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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Thank you