Novel Therapeutic Platform Targeting TLR4-Lipid Rafts for Treatment of Acute and Chronic Pain

Yury Miller, MD, PhD

Co-founder and Chief Scientific Officer, Raft Pharmaceuticals
yumiller@raftpharma.com
Professor, University of California San Diego
yumiller@ucsd.edu

Unmet Medical Need

Chronic Pain

- Following inflammation/nerve injury
- Annual cost $635B in the US
- ***Opiates, NSAIDs, gabapentinoid: Limited efficacy; adverse effects; abuse***

Postoperative Pain

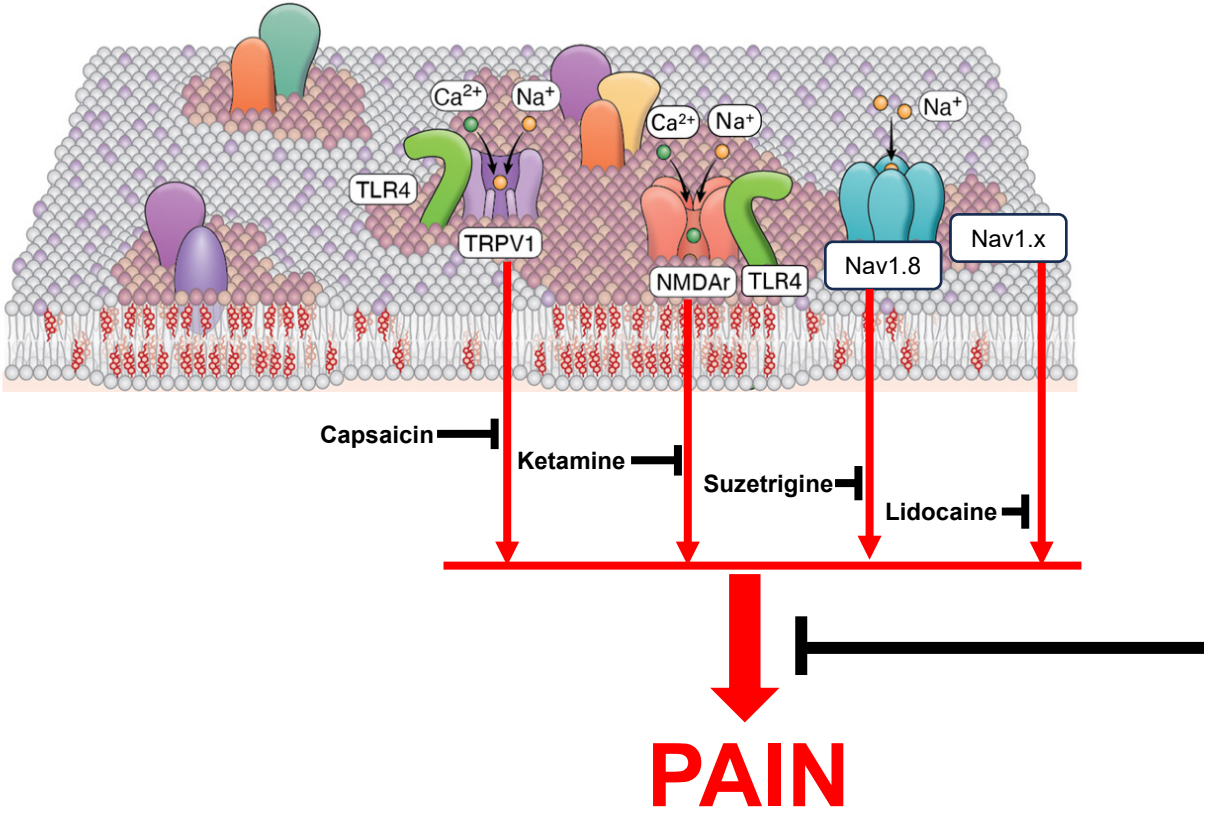
- Undertreated, impairing recovery
- Annual cost $38.4B in the US
- ***Opiates and NSAIDs: limiting side effects and addiction***

Migraine

- Second most common cause of disability in young/middle-aged women
- Annual cost $22B in the US
- ***CGRP/Triptan therapeutics 50% effective, adverse events***

RAFT PHARMACEUTICALS

Targeting TLR4-Lipid Rafts: Novel Approach to More Effective Analgesia



- **Individual pain target modulators exhibit partial/limited efficacy**
- **TLR4-Lipid Raft is the platform for assembly of multiple functional pain receptors and ion channels**
- **Targeting the entire TLR4-Lipid Raft creates the opportunity to inhibit ALL pain signaling, without affecting normal sensory or motor function**

TLR4-lipid rafts as a novel therapeutic target

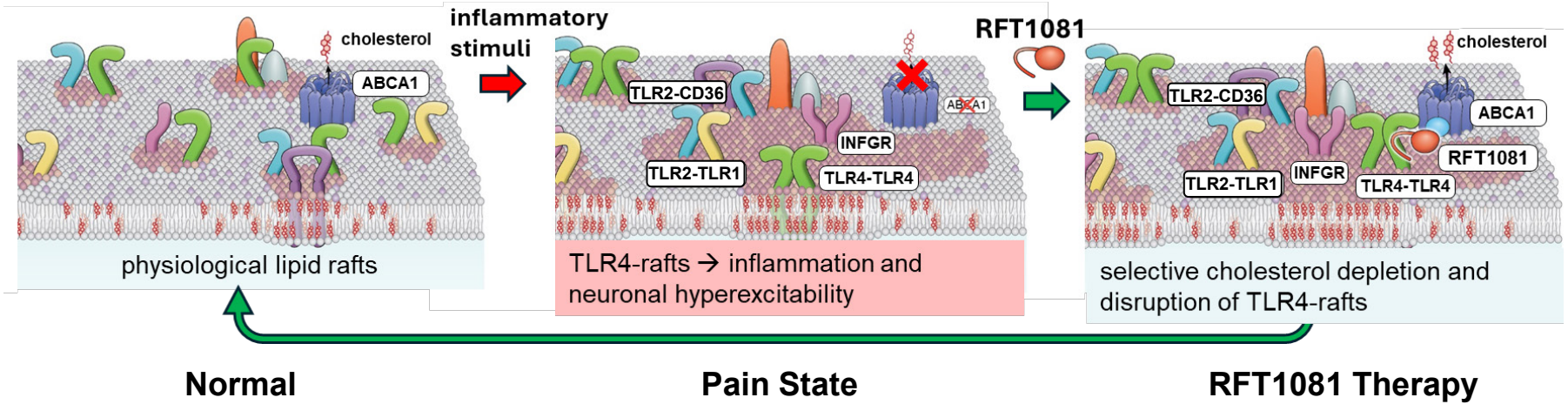
- Three major neuraxial cell types involved in pain processing and chronification express high levels of **TLR4**:
  - DRG (dorsal root ganglia) **nociceptive neurons**, but not low-threshold sensory or motor neurons
  - DRG **macrophages**
  - Spinal cord **microglia**

- In activated cells, **TLR4 is localized to lipid rafts** and forms functional complexes with other receptors:
  - TLR4-TLR4 homodimers (among others) in macrophages and microglia
  - TLR4-TRPV1, TLR4-NMDAr (among others) in neurons

Selective targeting of **TLR4-lipid rafts** by **RFT1081**

- RAFT's lead RFT1081 facilitates cholesterol removal from plasma membrane and reduces cholesterol-rich lipid rafts
- RFT1081 binds to TLR4 → targets cholesterol depletion machinery to cells with high TLR4-lipid rafts (e.g., DRG nociceptive neurons and macrophages / spinal microglia)
- Dissociation of TLR4-lipid rafts removes the assembly platform for inflammatory and nociceptive receptors and channels on neuraxial pain systems → benefit of polypharmacology vs. single pain target approaches
- Selective targeting of *TLR4-rafts* vs. *physiological lipid rafts* → beneficial safety profile

RFT1081: *Selective* cholesterol removal from cells with high expression of TLR4-lipid rafts



RAFT PHARMACEUTICALS

RFT1081 is a modified AIBP protein

1. Apolipoprotein A-I Binding Protein (AIBP; gene *APOA1BP* or *NAXE*) is an evolutionary conserved protein; secreted or intracellular
2. *APOA1BP* is a strong susceptibility locus for migraine
3. Reduced expression of endogenous AIBP in asthmatic bronchi and in glaucomatous retina
4. AIBP facilitates membrane cholesterol depletion from neurons, macrophages, microglia and endothelial cells
5. AIBP-mediated cholesterol depletion reduces lipid rafts and inhibits ectopic angiogenesis, vascular, neuro and pulmonary inflammation, and spontaneous activity in DRG neurons
6. **RFT1081 introduces a modification in AIBP molecule that facilitates its binding to TLR4 → *selective* targeting to TLR4-lipid raft expressing cells→ → *selective* disruption of receptors functioning within TLR4-lipid rafts**

Nature 2013; *Circ Res* 2017; *JCI Insight* 2018; *J Lipid Res* 2018; *Cell Rep* 2018; *Science* 2019; *Redox Biol* 2020; *mBio* 2020; *ATVB* 2020; *J Exp Med* 2021; *ATVB* 2021; *Clin Exp Allergy* 2022; *Pain* 2023; *J Neuroinflamm* 2024; *Antioxidants* 2024; *Brain Behav Immun* 2025; *Mol Therapy* 2025

RAFT PHARMACEUTICALS

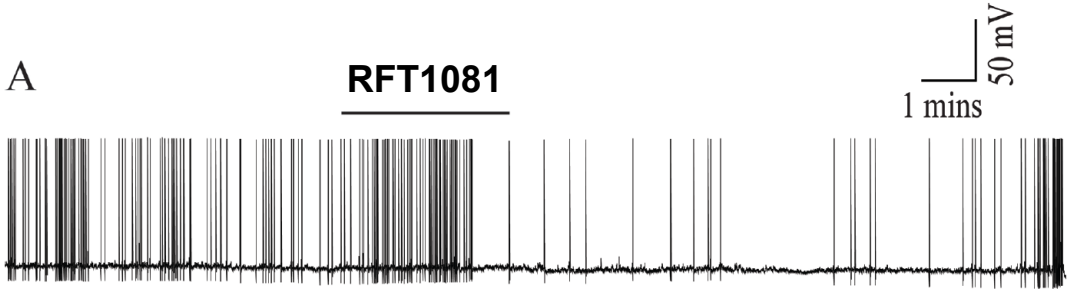
Target Product Profile for RFT1081

Property	Results
Potent modulator of TLR4 lipid rafts	• Binds to TLR4 to ensure selectivity • Depletes cholesterol and disrupts TLR4 rafts to block nociceptor excitability and neuroinflammation
Drug Characteristics	• Recombinant protein (32 kDa) • Modified apolipoprotein A-I binding protein (AIBP)
Therapeutic Targets	• Acute and chronic pain, migraine (additional studies in asthma control)
Administration Route	• Intrathecal (CIPN) • Intravenous (post-operative pain, migraine) • Subcutaneous (migraine)
Pharmacokinetics	• Relatively short exposure • Lasting pharmacodynamic effect
Efficacy	• Statistically significant efficacy in: ➢ human DRG neurons from painful dermatomes ➢ rat model of post-operative pain ➢ mouse model of migraine ➢ mouse model of chemotherapy-induced peripheral neuropathy
Preliminary Safety	• Up to 15-fold (intrathecal) or 4-fold (intravenous) efficacious dose* • Intrathecal delivery does not interfere with cancer chemo or immune therapy • Minimal in vitro immunogenicity
Intellectual Property	• Provisional filing 2021 • Specific claims in prosecution

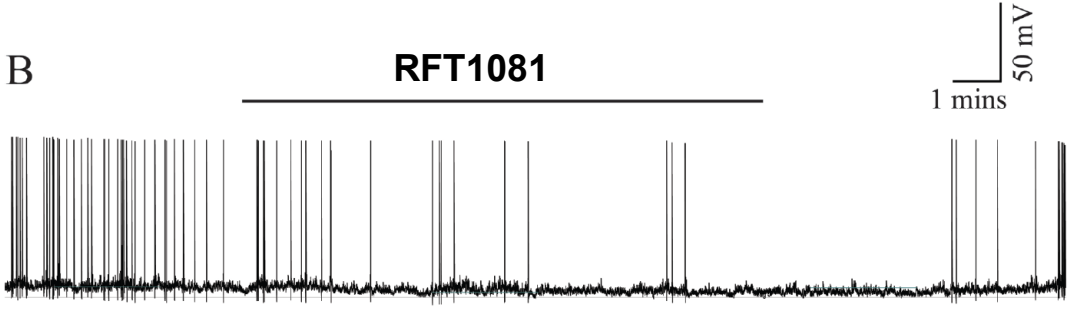
* Feasible margin based on therapeutic doses used; no microscopic findings in histopathology

RFT1081 inhibits spontaneous activity: validation of mechanism in **human** DRG neurons*

ipsilateral to root compression DRG neuron



contralateral DRG neuron primed with IL-6



* DRGs from patient tissues obtained during spinal reconstructive surgery

Pre-Operative Administration of RFT1081 Prevents Post-Operative Pain in Rats

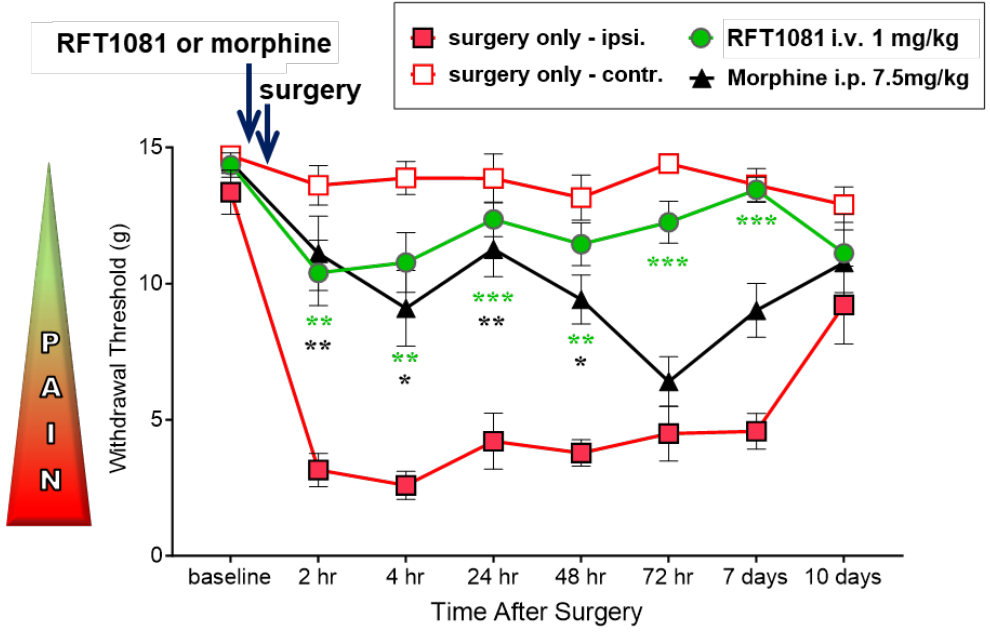


Figure:

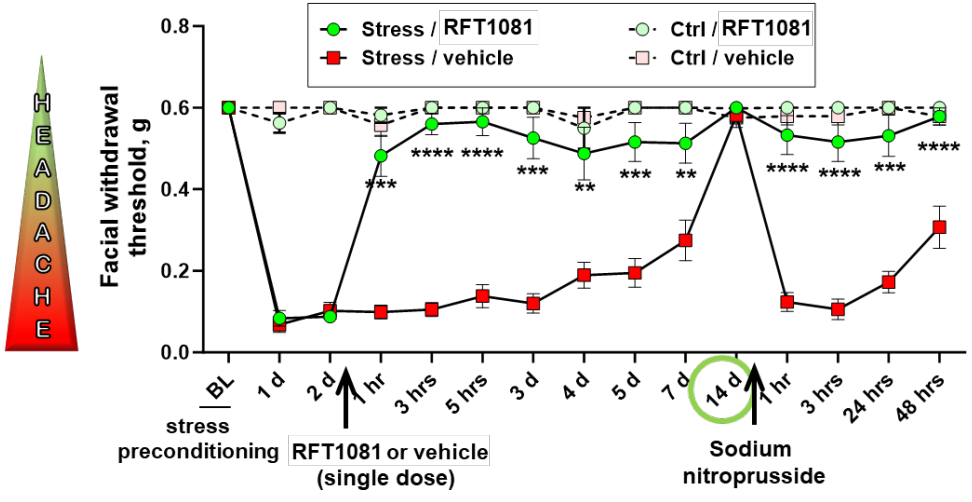
- Male Sprague-Dawley rats (n=6 per group, 2-way ANOVA)
- A single intravenous RFT1081 or intraperitoneal morphine (comparator/positive control) injection 30 min before paw incision surgery
- Von Frey testing of tactile allodynia on ipsilateral and contralateral paws (not all contralaterals shown)

Similar results with female rats

Open filed activity assay also shows superior analgesic effect of RFT1081 over morphine at 24h post-surgery

RFT1081 accelerated wound healing

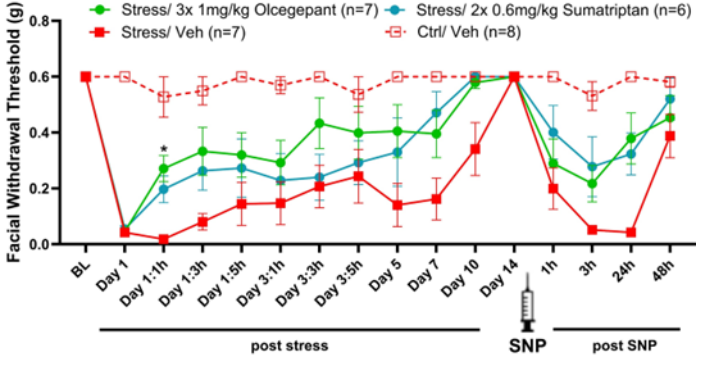
RFT1081 Reverses and Prevents Facial Allodynia in a Mouse Model of Migraine



Comparators:

Olcegepant, CGRP receptor antagonist

Sumatriptan, selective serotonin receptor agonist



Two-hit migraine model:

- Mice subjected to physical restraint stress (2h per day for 3 days) experience facial tactile sensitivity for at least 7 days, which subsides by day 14
- Facial allodynia is re-established by injection of NO generator (sodium nitroprusside) in stressed but not control mice

RFT1081 figure:

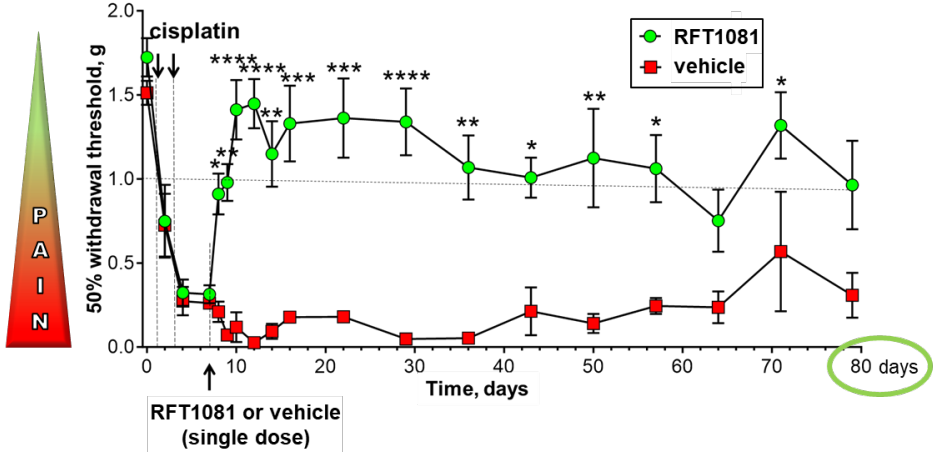
- Female mice (n=7-8 per group, 2-way ANOVA)
- A single intravenous RFT1081 injection on day 2 after the completion of the restraint stress regimen reversed stress-induced facial allodynia and prevented SNP-induced second-hit response

Similar results with male mice

Comparator figure: Female mice (n=7-8); Olcegepant was dosed on days 1, 2 and 3, and Sumatriptan on days 1 and 3.

In a different, mast cell activation model of migraine, RFT1081 prevented photophobia in mice

RFT1081 Produces a Long-lasting Reversal of Allodynia in a Mouse Model of Chemotherapy-induced Peripheral Neuropathy (Neuropathic Pain)



Mouse CIPN model:

- Two intraperitoneal injections of the chemotherapeutic cisplatin (days 1 and 3) induced polyneuropathy characterized by chronic hindpaw tactile allodynia.
- After allodynia was established, at day 7, a single intrathecal (similar to epidural) injection of RFT1081 reversed allodynia, with a therapeutic effect lasting over 2 months. Overall numbers of male animals per group were on days 0-22: n = 17 (RFT1081) and 12 (saline); days 29-79: n = 8 (RFT1081) and 3 (vehicle); two-way ANOVA

Dose response established

In a condition place preference assay, RFT1081 removed the preference to a gabapentin-paired compartment

Similar results with female mice

Efficacy in a paclitaxel CIPN model

Therapeutic effect of RFT1081 in mouse models of L5 spinal nerve ligation, intraplantar formalin and intrathecal LPS, and a rat model of intrathecal LPS

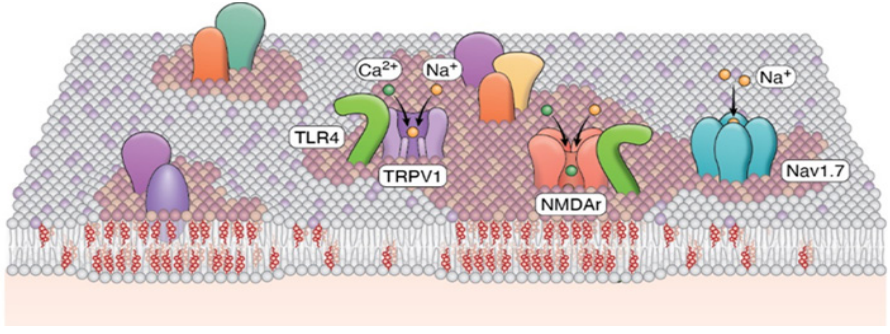
RAFT PHARMACEUTICALS

Unparalleled efficacy of RFT1081 in treatment of pain

***RFT1081* targets multiple pain phenotypes in which TLR4-rafts play pivotal role:**

- **long lasting, disease modifying therapeutic effect**
- **well tolerated**

RFT1081 targeting TLR4-rafts



Preclinical Behavioral Summary

Postoperative Pain

- **RFT1081: *Acute analgesia and prevention of persistent pain***
- ***Opiates and NSAIDs beset with limiting side effects and addiction***

Chronic Pain

- **RFT1081: *Inhibits polyneuropathy (CIPN) and development of chronic pain***
- ***Opiates, NSAIDs, gabapentinoids ineffective; adverse effects; abuse***

Migraine

- **RFT1081: *Efficacy in distinct pre-clinical models (potential to differentiate from other modalities)***
- ***CGRP/Triptan therapeutics 50% effective***

RAFT PHARMACEUTICALS

TLR4 = Toll-like receptor 4; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **CGRP** = calcitonin gene-related peptide; **CIPN**= chemotherapy-induced peripheral neuropathy

Tolerability of RFT1081 in rats and immunogenicity testing

- **Escalating dose range finding study of intrathecal RFT1081 in Sprague Dawley rats:**
  - There were no early deaths during the study, and no clinical observations were made
  - No changes were noted at gross necropsy
  - MTD was the highest dose administered
- **Ongoing 14-day toxicity and toxicokinetic study in Sprague Dawley rats**
- **Ongoing second species selection study in dogs and non-human primates**
- ***In vitro* immunogenicity assessment of RFT1081:**
  - In PBMC from 50 human donors incubated with RFT1081, T cell activation markers and proliferation were minimal and comparable with approved non-immunogenic biologics
- **Mouse drug-drug interaction study: Intrathecal RFT1081 did not affect anti-tumor therapy**:
  - Cisplatin (chemotherapy) in treatment of A549 lung carcinoma
  - Anti-PD1 antibody (immunotherapy) in treatment of C56 colon cancer

RAFT PHARMACEUTICALS

Corporate Summary

Novel Therapeutic Platform Targeting TLR4-Lipid Rafts for Treatment of Acute and Chronic Pain

- **Novel therapeutic platform**:
  - ✓ Lead identified is efficacious in multiple pain indications
  - ✓ MoA poised to be disruptive for current pain therapy
- **Favorable pre-clinical profile**:
  - ✓ Long-lasting therapeutic efficacy suggests **disease modifying MoA**
  - ✓ Well-tolerated in mice and rats
- **Developing IP portfolio** to support lead candidate
- **Funding history**:
  - ✓ NIH SBIR/STTR grants to validate lead assets for clinical development
  - ✓ No equity investment or current debt

Seeking strategic investors and Pharma development/commercialization partners

Team

FOUNDERS

Co-founder/CSO

Yury Miller, MD, PhD

- Professor at UC San Diego
- Lipid and cholesterol metabolism, oxidized lipids
- Discovered role of AIBP in regulation of inflammatory signaling

Co-founder/BoD

Tony Yaksh, PhD

- Professor at UC San Diego
- Pioneer in spinal mechanisms of pain and analgesia
- Significant experience in preclinical studies including performance of pivotal small and large animal trials

SENIOR MANAGEMENT

COO

Graham Beaton, PhD

- Experienced entrepreneur
- Expert in drug discovery and translational R&D
- Program leadership

Head of Drug Development

Yakov Kogan, PhD, MBA

- Led 11 drug development programs (from R&D to BLA)
- BD & corporate management
- Former CEO of Cleveland BioLabs (NASDAQ: CBLI) and CEO/COO/EVP/SVP in several private drug dev. companies

ACADEMIC/CLINICAL COLLABORATORS

Patrick Dougherty, PhD
MD Anderson Cancer Center
Mechanisms of acute and chronic pain, including neuropathic pain related to cancer and CIPN

Gregory Dussor, PhD
University of Texas Dallas
Mechanisms and therapeutic targets for migraine headache

Mark Wallace, MD
UC San Diego
Pain management/ co-director of Altman Clinical and Translational Research Institute

Gregory Botta, MD, PhD
UC San Diego
Physician-scientist, specializing in Gastrointestinal Tumor Medical Oncology

Andrei Osterman, PhD
Sanford Burnham Prebys Inst.
Protein engineering, manufacturing process development and scale-up, analytical methods

A unique blend of mature science, entrepreneurial talent and strong prospects of clinical development

BIBLIOGRAPHY

Restoring **AIBP** expression in the retina provides neuroprotection in glaucoma. Ju WK, … Miller YI, Choi SH. *Mol Ther*. 2025 May 9:S1525-0016(25)00379-X.

ApoA-I binding protein (**AIBP**) regulates transient receptor potential vanilloid 1 (TRPV1) activity in rat dorsal root ganglion neurons by selective disruption of toll-like receptor 4 (TLR4)-lipid rafts. Li Y, … Yaksh TL, Miller YI, Kosten TA, Dougherty PM. *Brain Behav Immun*. 2025;123:644-655.

AIBP controls TLR4 inflammarafts and mitochondrial dysfunction in a mouse model of Alzheimer's disease. Kim YS, … Miller YI. *J Neuroinflammation*. 2024 Sep 28;21(1):245.

AIBP Protects Müller Glial Cells Against Oxidative Stress-Induced Mitochondrial Dysfunction and Reduces Retinal Neuroinflammation. Choi S, … Miller YI, Ju WK. *Antioxidants* (Basel). 2024 Oct 17;13(10):1252.

Restoring AIBP expression in the retina provides neuroprotection in glaucoma. Ju WK, … Miller YI, Choi SH. *bioRxiv* [Preprint]. 2023 Dec 29:2023.10.16.562633. doi: 10.1101/2023.10.16.562633.

AIBP regulates TRPV1 activation in chemotherapy-induced peripheral neuropathy by controlling lipid raft dynamics and proximity to TLR4 in dorsal root ganglion neurons. Navia-Pelaez JM, … Dougherty PM, Yaksh TL, Miller YI. *Pain*. 2023 Jun 1;164(6):e274-e285.

Reduced **AIBP** expression in bronchial epithelial cells of asthmatic patients: Potential therapeutic target. Miller M… … Broide DH, Miller YI. *Clin Exp Allergy*. 2022 Aug;52(8):979-984.

Normalization of cholesterol metabolism in spinal microglia alleviates neuropathic pain. Navia-Pelaez JM, … Yaksh TL, Miller YI. *J Exp Med*. 2021 Jul 5;218(7):e20202059.

AIBP protects retinal ganglion cells against neuroinflammation and mitochondrial dysfunction in glaucomatous neurodegeneration. Choi SH, … Miller YI, Ju WK. *Redox Biol*. 2020 Oct;37:101703.

Lipid rafts in glial cells: role in neuroinflammation and pain processing. Miller YI, Navia-Pelaez JM, Corr M, Yaksh TL. *J Lipid Res*. 2020 May;61(5):655-666.

AIBP augments cholesterol efflux from alveolar macrophages to surfactant and reduces acute lung inflammation. Choi SH, … Miller YI. *JCI Insight*. 2018 Aug 23;3(16):e120519.

Inhibition of Neuroinflammation by **AIBP**: Spinal Effects upon Facilitated Pain States. Woller SA, … Yaksh TL, Miller YI. *Cell Rep*. 2018 May 29;23(9):2667-2677.

AIBP protects against metabolic abnormalities and atherosclerosis. Schneider DA, … Miller YI. *J Lipid Res*. 2018 May;59(5):854-863.

Control of angiogenesis by **AIBP**-mediated cholesterol efflux. Fang L, … Miller YI. *Nature*. 2013 Jun 6;498(7452):118-22.