



Modulation of Lipid Rafts as a Novel Therapeutic Platform to Treat Disease

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Executive Summary

The Problem:

- Disease phenotypes are often complex and heterogeneous
- Single target modalities often have limited efficacy and clinical benefit

The RAFT Solution

- Disease dysfunction is often accompanied by activated cell populations *via* lipid rafts
- ***Selective modulation of activated lipid rafts affects multiple signaling pathways predicting improved efficacy***
- Selective lipid raft modulation is possible through metabolic reprogramming of activated cells
 - Targeted cholesterol depletion
- Technology licensed to RAFT Pharmaceuticals LLC from University California San Diego (UCSD)
- Lead RFT1081
- First application to treat multiple pain disorders

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-mediated cholesterol depletion reduces lipid rafts and inhibits ectopic angiogenesis, vascular, neuro and pulmonary inflammation, and spontaneous activity in DRG neurons
5. **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

Pain – A Continuing Unmet Medical Need

Chronic Pain

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

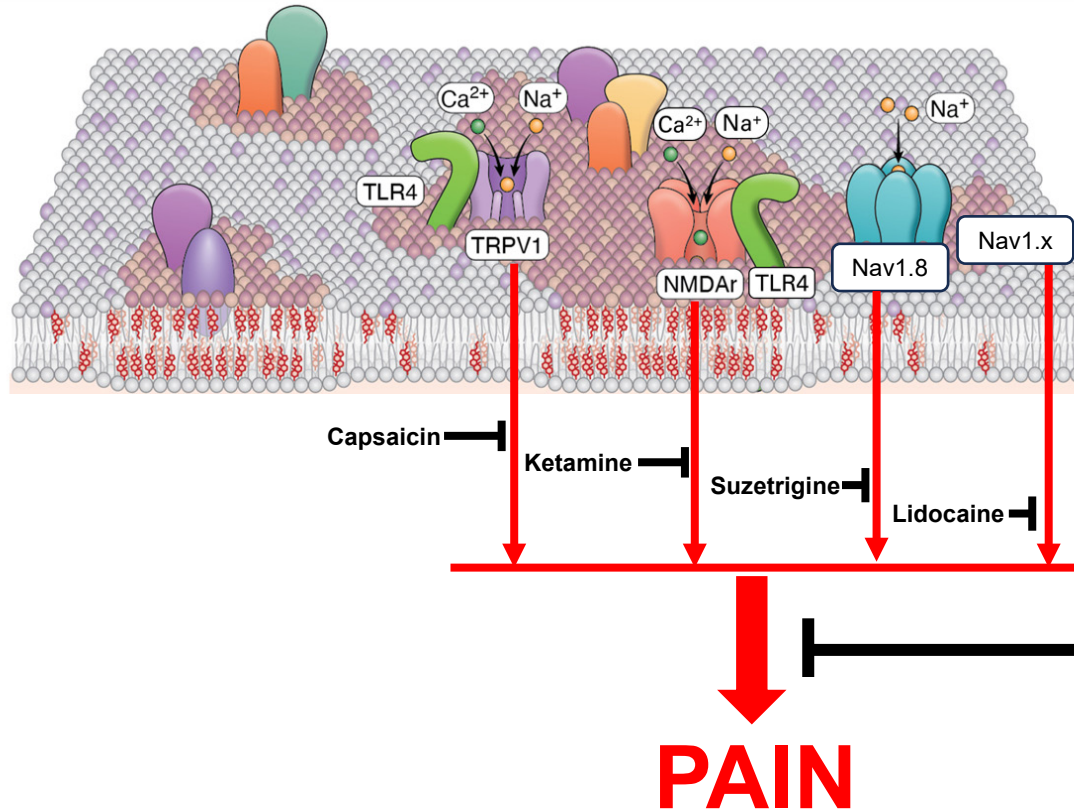
Postoperative Pain

- 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***

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

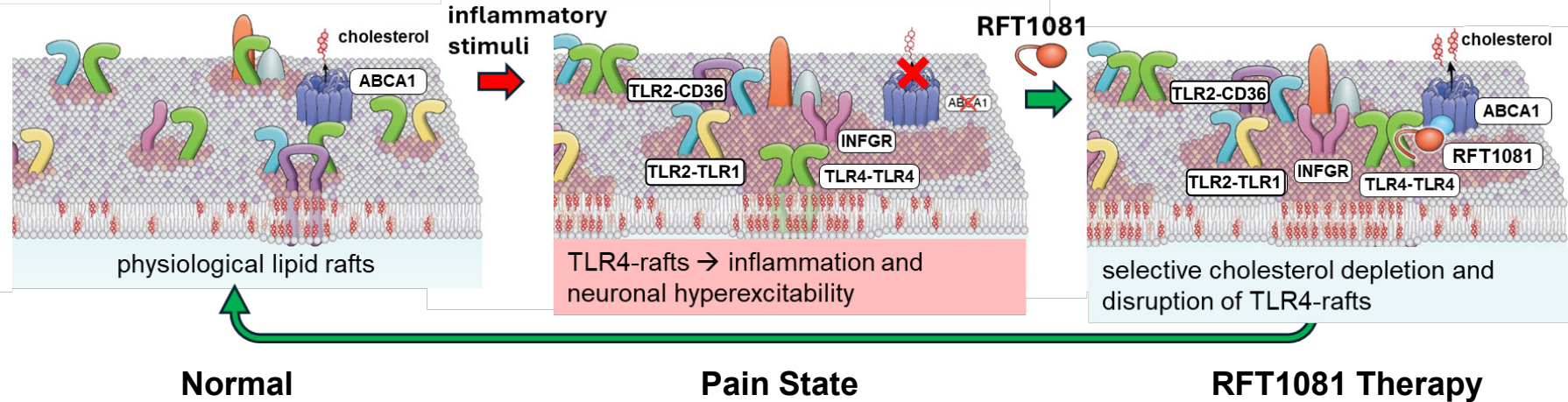
TLR4-lipid rafts as a novel therapeutic target

- Three major neuraxial cell types involved in pain processing and chronification express high levels of **TLR4**:
 - DRG (dorsal root ganglia) **nociceptive neurons**
 - DRG **macrophages**
 - Spinal cord **microglia**
- In activated cells, **TLR4 is localized to lipid rafts** and forms functional receptor complexes:
 - TLR4-TLR4 homodimers (among others) in macrophages and microglia
 - TLR4-pain receptors: TLR4-TRPV1, TLR4-NMDAr (among others) in neurons

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

- RFT1081 facilitates cholesterol removal from plasma membrane and reduces cholesterol-rich lipid rafts
- RFT1081 binds to TLR4
 - **Targets** cholesterol depletion in cells with high TLR4-lipid rafts (neuraxial cells)
 - **Dissociates** TLR4 complexes and associated pain receptors
 - **Single target** with the benefit of polypharmacology
- 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

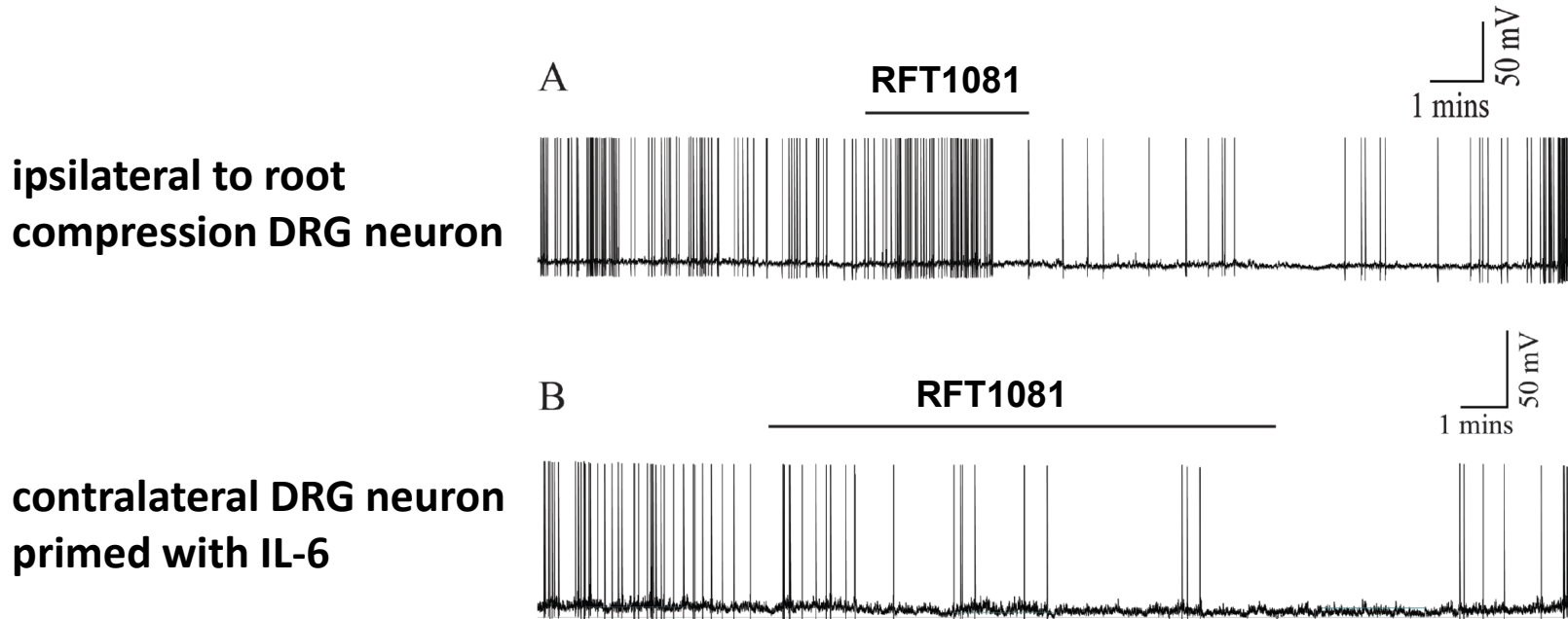


RFT1081 Profile

Property	Results
Potent modulator of TLR4 lipid rafts	<ul style="list-style-type: none"> • Binds to TLR4 to ensure selectivity • Depletes cholesterol and disrupts TLR4 rafts to block nociceptor excitability and neuroinflammation
Drug Characteristics	<ul style="list-style-type: none"> • Recombinant protein (32 kDa) • Modified apolipoprotein A-I binding protein (AIBP)
Therapeutic Targets	<ul style="list-style-type: none"> • Acute and chronic pain, migraine (additional studies in asthma control)
Administration Route	<ul style="list-style-type: none"> • Intrathecal (CIPN) • Intravenous (post-operative pain, migraine) • Subcutaneous (migraine)
Pharmacokinetics	<ul style="list-style-type: none"> • Relatively short exposure • Lasting pharmacodynamic effect
Efficacy	<ul style="list-style-type: none"> • Statistically significant efficacy in: <ul style="list-style-type: none"> ➢ human DRG neurons from painful dermatomes ➢ rat model of post-operative pain ➢ mice models of migraine ➢ mouse model of chemotherapy-induced peripheral neuropathy
Preliminary Safety	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Exclusivity for Composition of Matter anticipated from 2021 • Additional protection for methods in pain from 2023

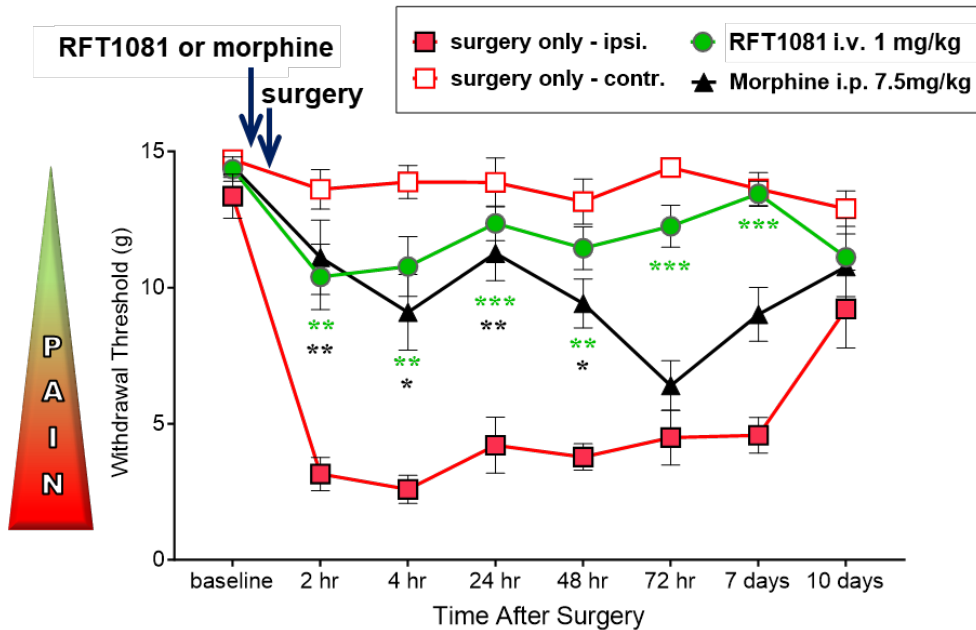
* Feasible margin based on therapeutic doses used; no microscopic findings in histopathology

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



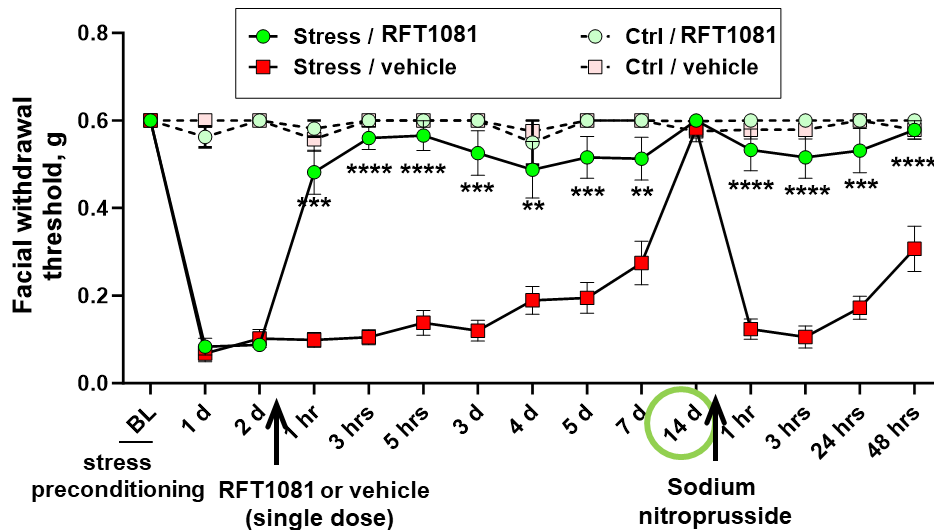
* DRGs from patient tissues obtained during spinal reconstructive surgery

RFT1081 Prevents Post-Operative Pain in Rats



- 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 is effective in neuropathic pain (SNI model) – agent for neuropathic pain treatment and the prevention of persistent pain following surgery

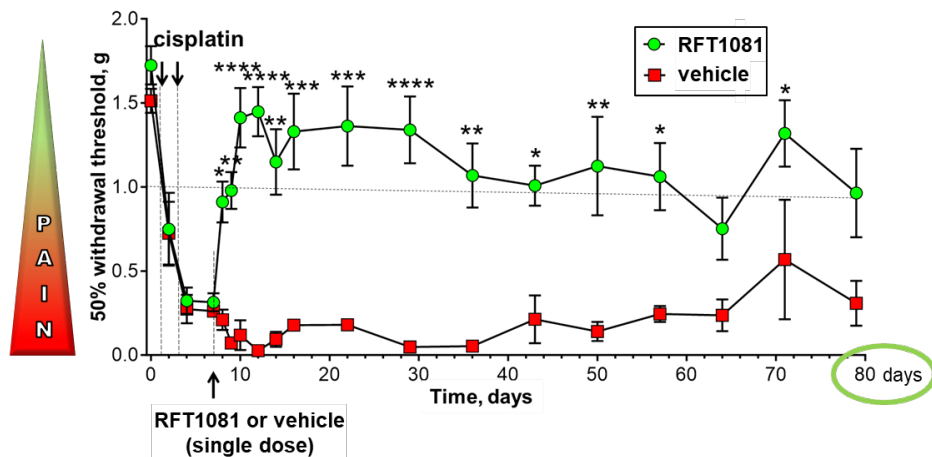
RFT1081 Inhibits Longer Term Migraine Behaviors in Mice



Two-hit migraine model:

- RFT1081 reverses facial allodynia induced by stress in mice
- RFT1081 prevents the induction of migraine behaviors following sodium nitroprusside challenge
- Female mice (n=7-8 per group, 2-way ANOVA)
- Similar results with male mice
- Comparison to standard of care agents (*Olcegepant*, *Sumatriptan*) suggests superior efficacy
- RFT1081 is effective in the photophobia model in mice

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



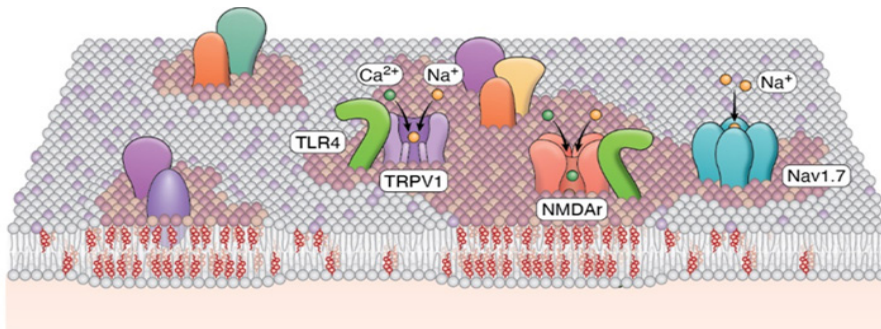
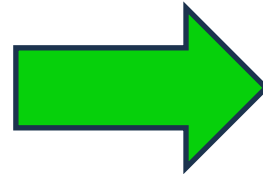
- Polyneuropathy induced by two intraperitoneal injections of cisplatin (days 1 and 3) to establish hindpaw allodynia
- At day 7, a single intrathecal (similar to epidural) injection of RFT1081 reversed allodynia, with a therapeutic effect lasting over 2 months
[Overall numbers of male animals per group were on days 0-22: n = 17 (RFT1081) and 12 (saline); days 29-79: n = 8 (RFT1081) and 3 (vehicle); two-way ANOVA]
- In a condition place preference assay, RFT1081 removed the preference to a gabapentin-paired compartment
- Dose response with female mice
- Effective in a paclitaxel CIPN model
- These data and efficacy of RFT1081 in mouse models of L5 spinal nerve ligation, intraplantar formalin and intrathecal LPS, and a rat model of intrathecal LPS establish a case for inhibition of neuropathic pain behaviors

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

**NOVEL THERAPEUTIC PLATFORM TARGETING LIPID RAFTS FOR TREATMENT OF DISEASE
FIRST DEMONSTRATION IN THE TREATMENT OF ACUTE AND CHRONIC PAIN
OTHER DEVELOPING APPLICATIONS**

- **RFT1081:**
 - ✓ 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***

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

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