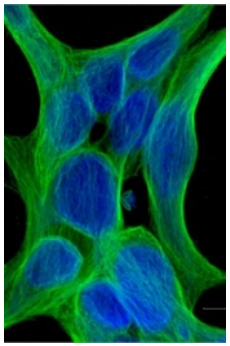
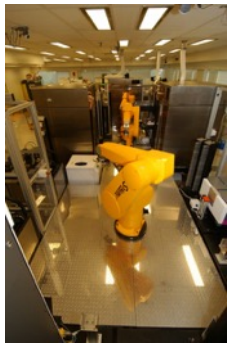
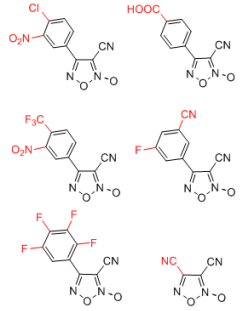
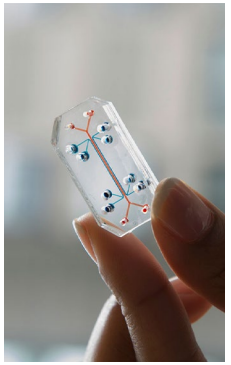
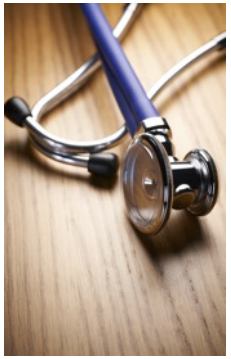
NIH HEAL INITIATIVE

NCATS Update on HEAL Research Collaborations

Dr. Christopher Austin, Director, National Center for Advancing Translational Sciences
Dr. Donald C. Lo, Director, Therapeutic Development Branch, Division of Preclinical Innovation National Center for Advancing Translational Sciences

Steps, Costs, and Time of the Drug Development Process

(using small molecule drugs as an example)

Identify disease mechanism	Create testing system	Test chemicals in system	Modify (chemistry) for human use	Test in preclinical models	Test in humans
					
Basic Research	Assay Development	Screening	Medicinal Chemistry	Preclinical Development	Clinical Development

Target ID — $50-100K

Lead discovery — $500K-1M

Preclinical and early clinical — $5-10M

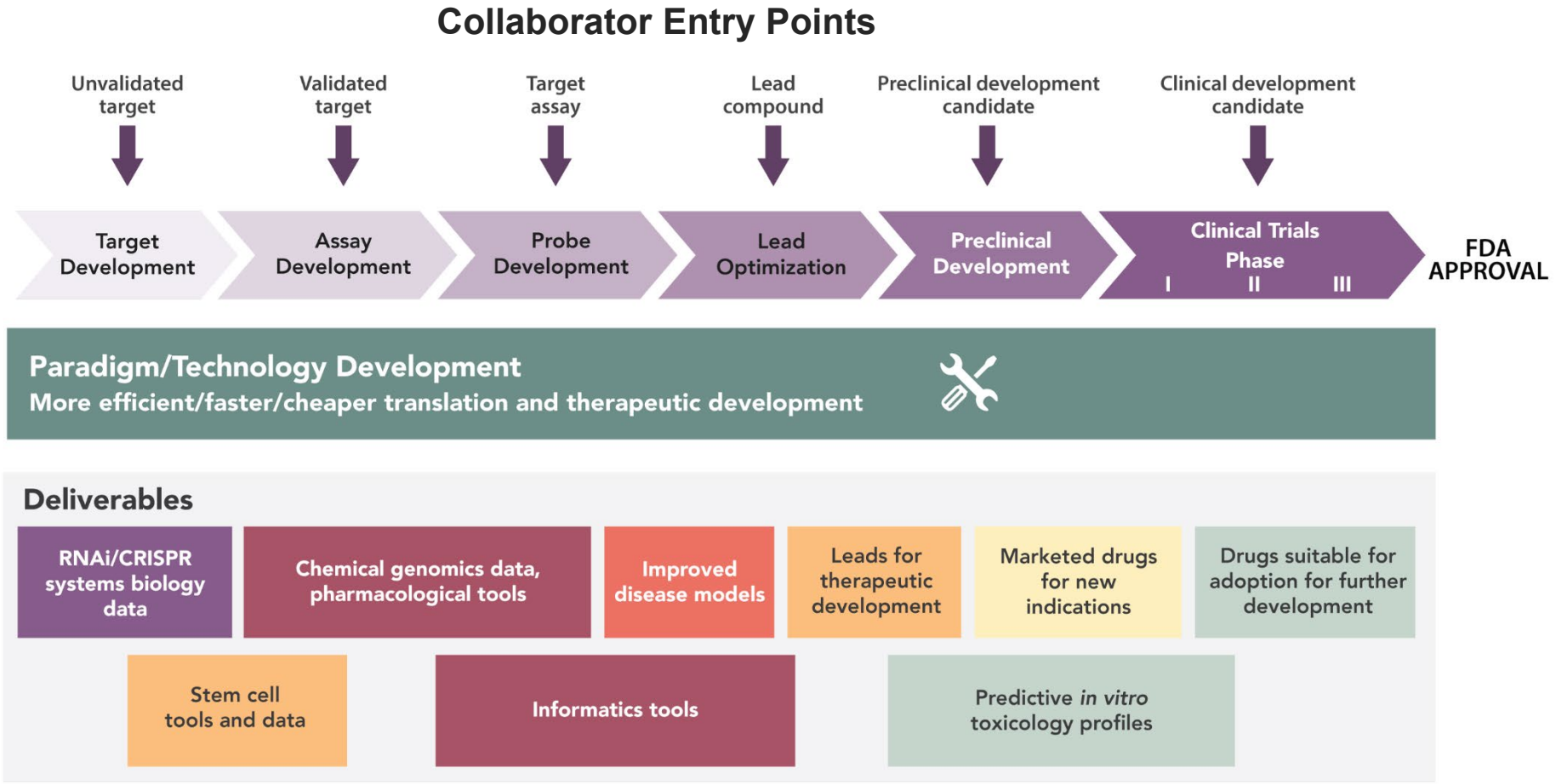
Late clinical — $50-100M

3 – 6 years

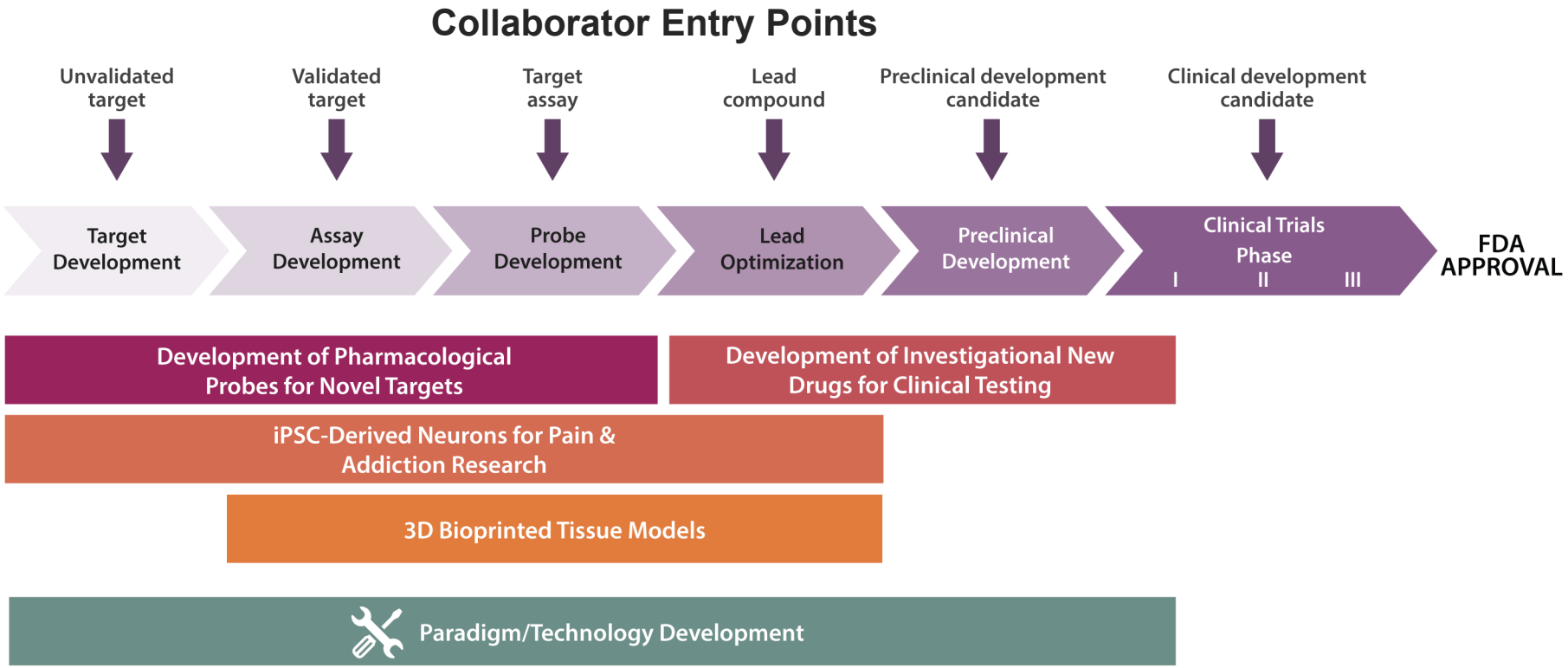
6 - 7 years

Preclinical Innovation at NCATS:
Established COLLABORATIVE Operational Model

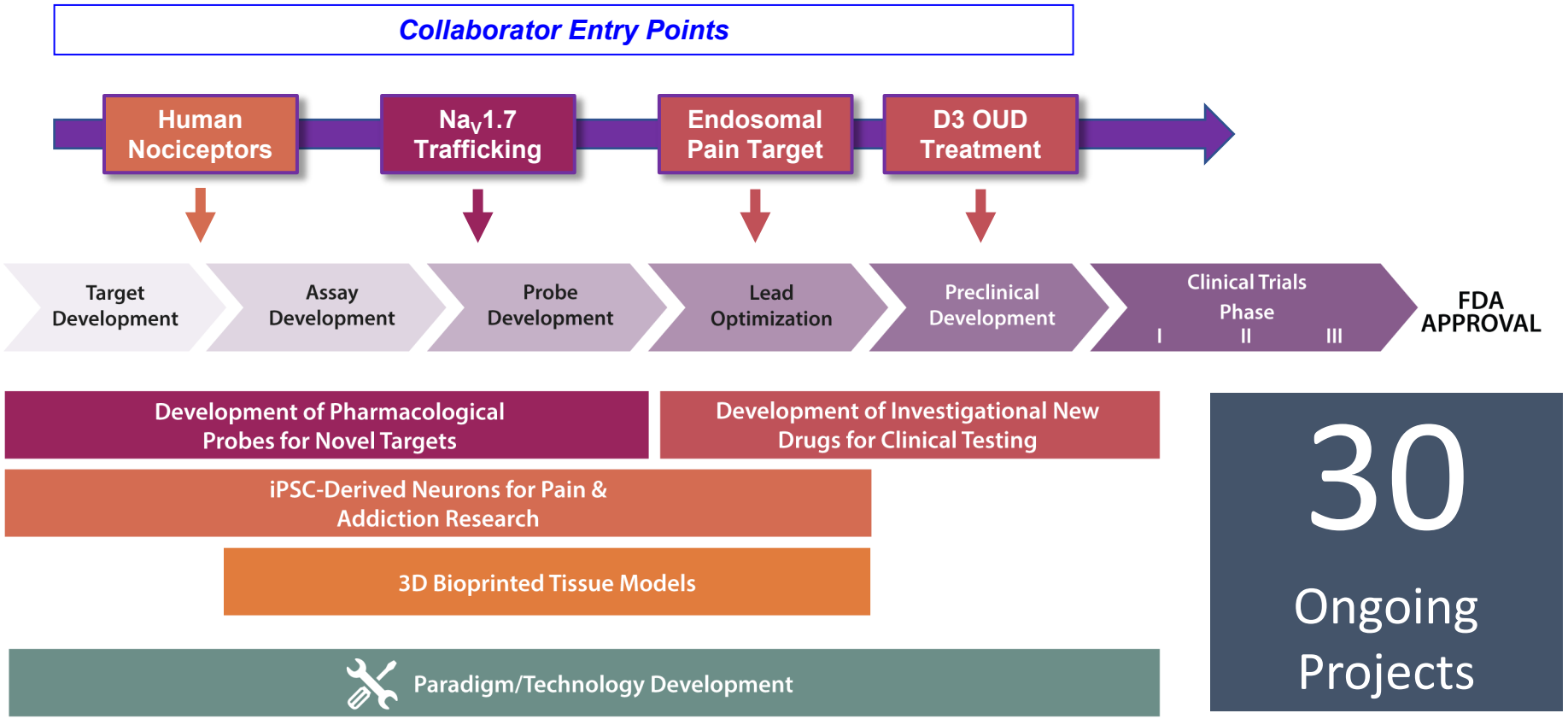
Collaborators and NCATS scientists form joint project teams with milestones; no $ issued or received



Preclinical Innovation at NCATS:
Leveraged for the HEAL Initiative



Preclinical Innovation at NCATS:
Current HEAL Initiative projects



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Ongoing Projects

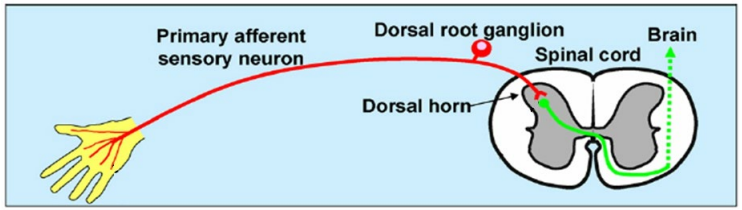
iPSC-Derived Neurons for Pain & Addiction Research

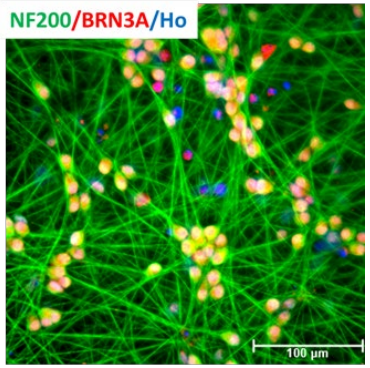
Developing Human Nociceptor-Selective Analgesics

Lead Collaborator: **Clifford J. Woolf**
Affiliation: **Boston Children's Hospital; Harvard Medical School**

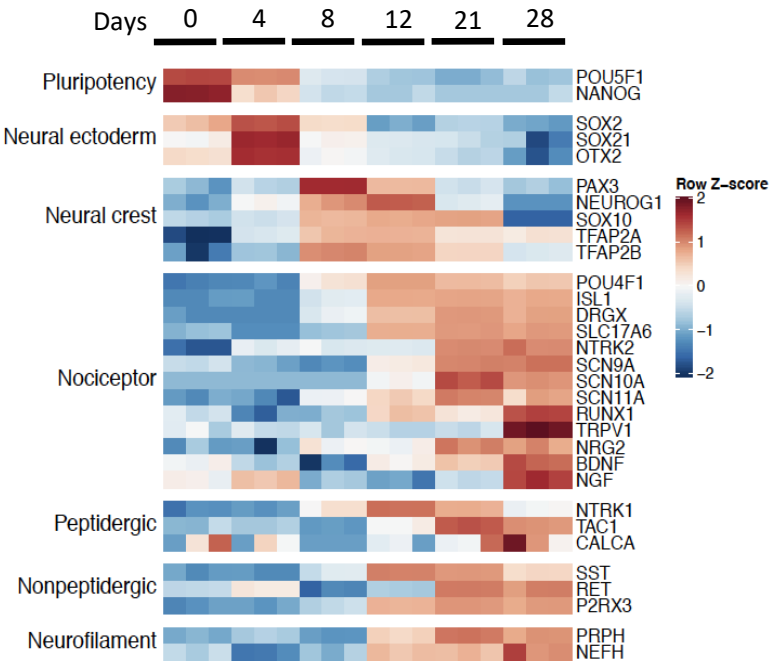
Background

- **Critical need to develop new pain therapeutics in human cells and in the relevant neuronal cell types such as nociceptors**
- Dr. Ilyas Singeç and the NCATS Stem Cell Translation Laboratory developed new protocol for nociceptor differentiation from human iPSCs
- Protocol is reproducible, scalable and has been automated to produce billions of human cells for high-throughput experiments and disease modeling
- Morphology and molecular signature of iPSC-nociceptors recapitulate that of *in vivo* DRG neurons





Step-wise and controlled differentiation (RNA-seq)



Nociceptor gene expression signature

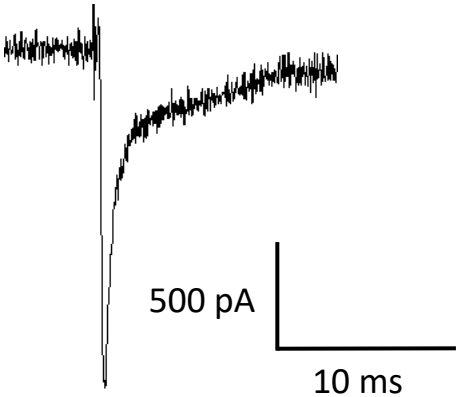
iPSC-Derived Neurons for Pain & Addiction Research

Developing Human Nociceptor-Selective Analgesics

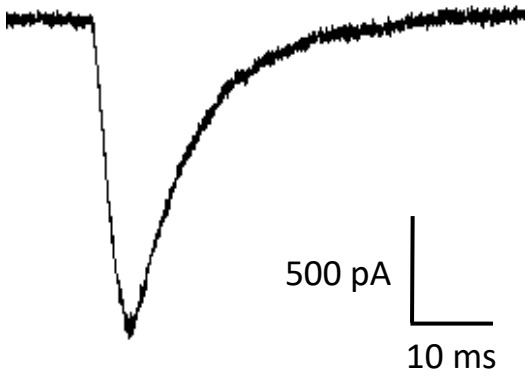
Lead Collaborator: **Clifford J. Woolf**
Affiliation: **Boston Children's Hospital; Harvard Medical School**

- **New human iPSC-nociceptors are first to natively express $Na_V1.7$ and $Na_V1.8$ sodium channels**
- **$Na_V1.7$/$Na_V1.8$ are human-validated pain drug targets**
  - Loss-of-function mutations reduce pain; gain-of-function mutations results in neuropathic pain
- ***Appropriate human cell models have otherwise been lacking for $Na_V1.7$/$Na_V1.8$ drug development***

$Na_V1.7$ current



$Na_V1.8$ current



data from Jaehoon Shim

Goals:

- HTS to identify nociceptor selective inhibitors
- Disease modeling for new target identification and validation
- Additional protocols under development to generate other relevant cell types from human iPSCs

Current status:

- External validation of NCATS iPSC-nociceptors by Woolf Lab
- Robotic nociceptor production
- **Distribution of differentiated nociceptors to numerous pain research and translation labs**

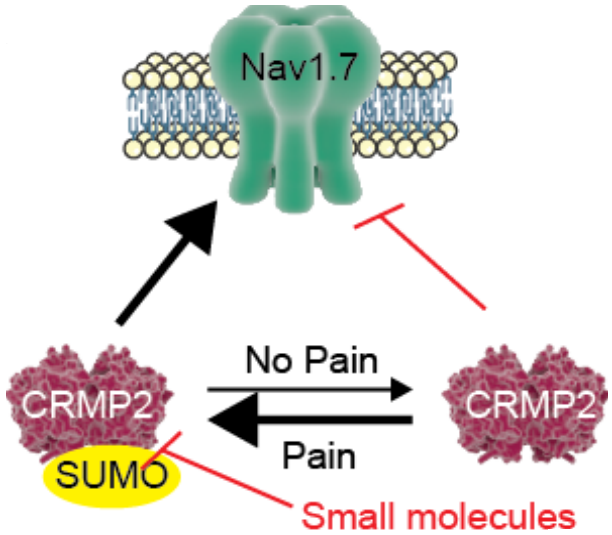
Development of Pharmacological Probes for Novel Targets

Optimization of Allosteric Regulators of the $Na_V1.7$ Sodium Channel for Chemotherapy-induced Peripheral Neuropathy (CIPN)

Lead Collaborator: **Rajesh Khanna, PhD, U Arizona College of Medicine**
Affiliation: **Regulonix, LLC**

Therapeutic Hypothesis

- Ion channel targets have been challenging to drug
- Alternative strategy for blocking NaV1.7 function = reducing pain sensation is to prevent its trafficking to the neuronal plasma membrane
    - *CRMP2 is essential trafficking protein for NaV1.7*
    - *SUMOylation of CRMP2 is required for membrane targeting*
- ➢ **Goal is to block SUMOylation of CRMP2 with small molecule drug-like compounds**
- Drug lead candidate already demonstrating efficacy in animal model



Regulonix
Non-Opioid Drugs for Chronic Pain

Dib-Hajj *et al.*, Nat. Rev. Neurosci. (2013); Dustrude *et al.*, J. Biol. Chem. (2013)

Development of Pharmacological Probes for Novel Targets

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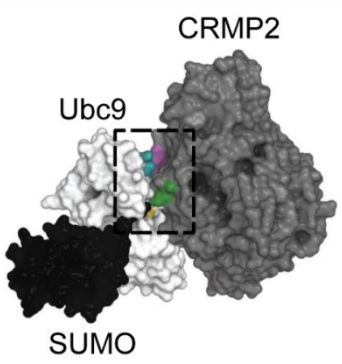
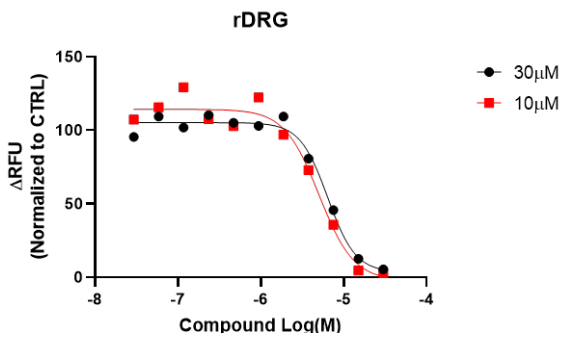
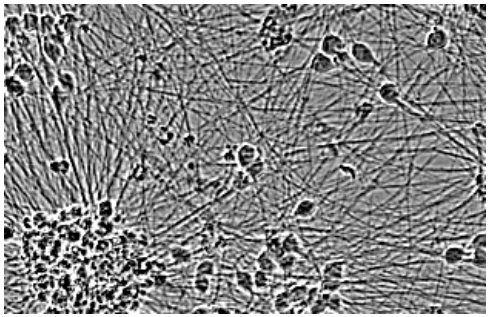
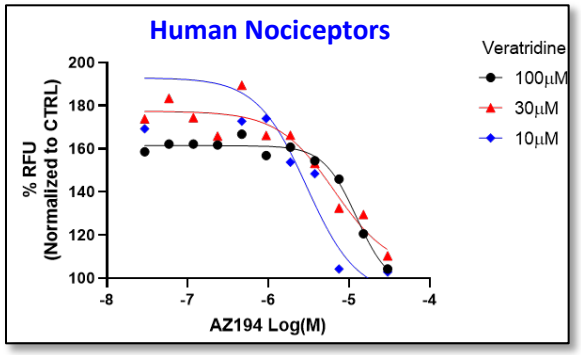




Initial compounds and rat dorsal root ganglion culture data reproduced at NCATS





Efficacy of hit compounds validated in human iPSC nociceptors

Goals:

- ✓ Verify and validate target mechanism of action
- Medicinal chemistry to optimize lead compound for drug-like properties
- Test therapeutic hypothesis in animal pain models
- ***If successful will be potential for further preclinical development towards IND***

Current status:

- Synthesized lead series compounds in-house and reproduced mechanism.
- **Validated mechanism using human iPSC-nociceptors natively expressing Nav1.7 sodium channels**

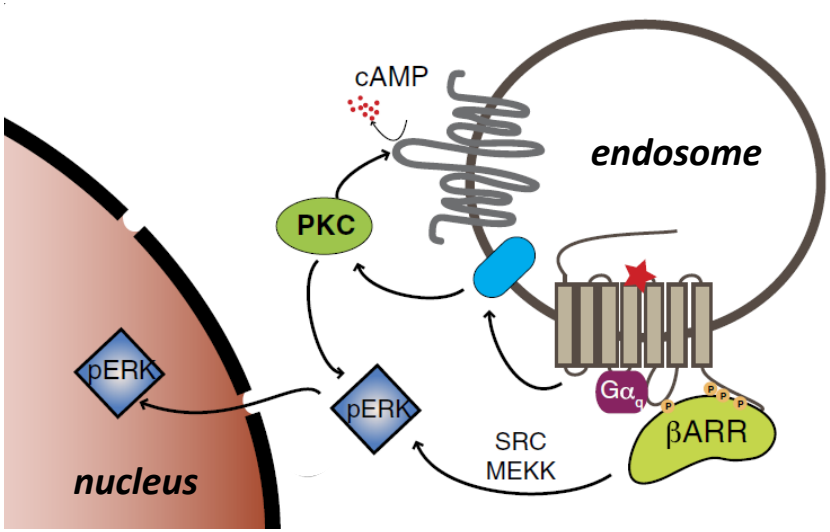
Development of Investigational New Drugs for Clinical Testing

Targeting endosomal GPCR (eGPCR) signaling platforms for the treatment of chronic pain

Lead Collaborator: **Nigel Bunnett, PhD**
Affiliation: **New York University and Endosome Therapeutics, Inc.C**

Therapeutic Hypothesis

- Several GPCRs including the substance P/neurokinin 1 receptor (NK1R) mediate pain transmission
- Yet antagonists of NK1Rs and other pain-mediating GPCRs failed to show efficacy in human clinical trials
- Following activation, NK1Rs are endocytosed and *continue to mediate pain transmission* from this intracellular compartment
- **Endosomal-targeted NK1R antagonist will be effective for the treatment of chronic pain**



NK1Rs continue to mediate pain transmission after endocytosis

Bunnett *et al*. Sci. Trans. Med. (2017); Nature Nano (2019)

Development of Investigational New Drugs for Clinical Testing

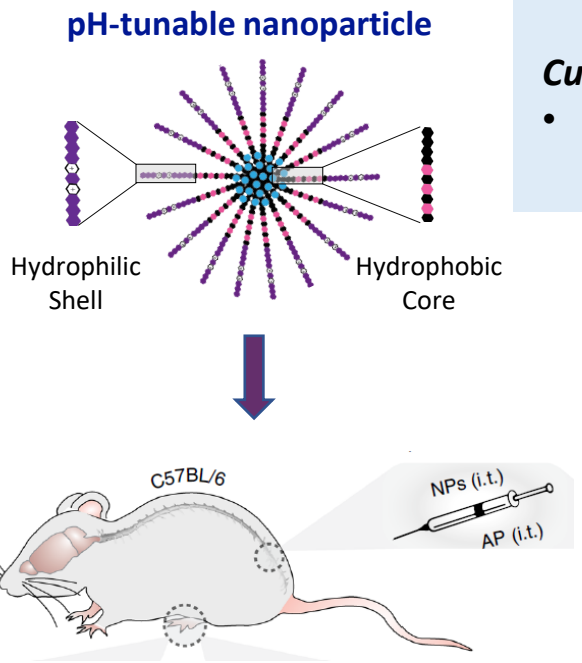
Targeting endosomal GPCR (eGPCR) signaling platforms for the treatment of chronic pain

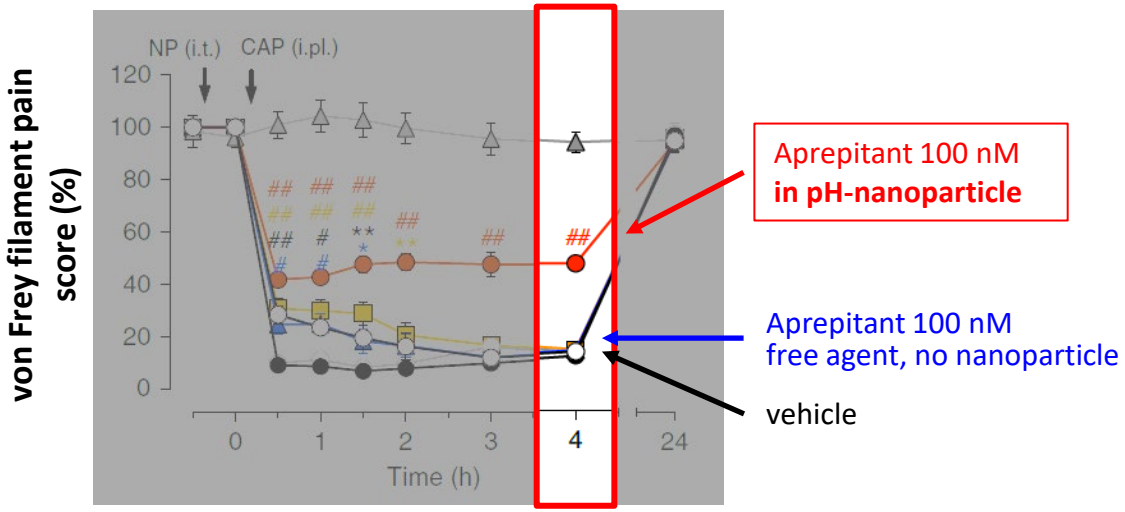
Goal:

- **Re-formulate NK1R antagonist aprepitant** (FDA-approved only for chemotherapy-related and postoperative nausea) **by targeting to endosomes via pH-tunable nanoparticles which release drug upon acidification**
- If successful will complete IND-enabling studies for entry into clinical testing

Current status:

- Validating *in vivo* studies in independent lab and optimizing nanoparticle formulation





Development of Investigational New Drugs for Clinical Testing

Selective dopamine D3 receptor antagonists for the treatment of OUD

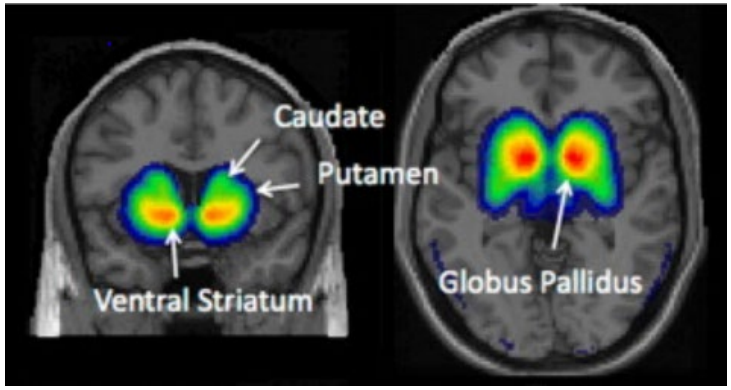
Lead Investigator: **Amy Newman, PhD, NIDA**
Collaborator: **Braeburn Inc.**

Therapeutic Hypothesis

- Drugs of abuse activate the dopamine system in the mesolimbic reward centers of the brain
- D3 dopamine receptors in the *nucleus accumbens* show elevated expression in addiction
- Selective D3R antagonists effective in preclinical models of substance use disorders (Heidbreder and Newman, 2010)

➢ **Co-administration D3 receptor antagonists should mitigate opioid dependence *without* interfering with analgesia**

➢ **On NIDA's "ten most wanted" list** (Rasmussen *et al.* 2018)



Human PET imaging with selective D3R antagonist; ventral striatum includes *n. accumbens.* Slifstein *et al.,* 2014.

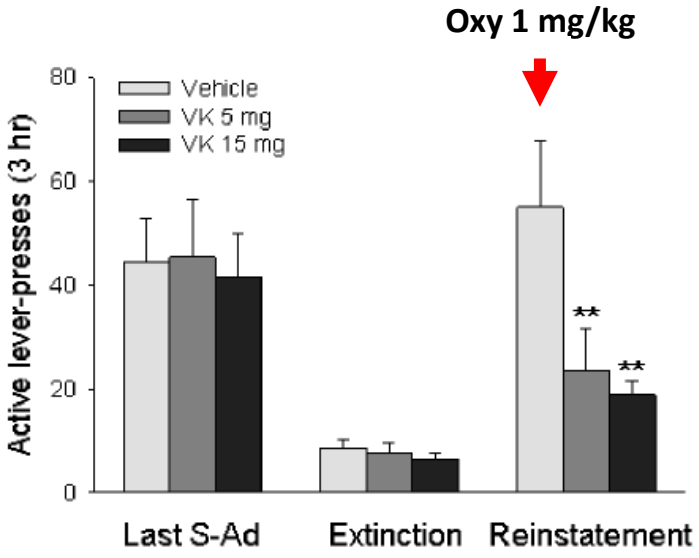
Challenge: 1st generation D3R antagonists potentiated cocaine-induced **blood pressure increase**; further development by pharma including for smoking cessation halted

Development of Investigational New Drugs for Clinical Testing

Selective dopamine D3 receptor antagonists for the treatment of OUD

Newman/NIDA/Braeburn selective D3R antagonist lead candidate VK4-116:

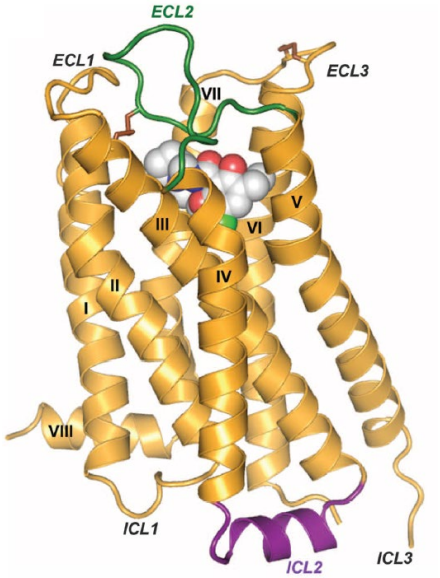
- ***Does not***
  - ✓ affect blood pressure or heart rate
  - ✓ bind to opioid receptors
  - ✓ affect locomotor activity and "normal" motivation
  - ✓ reduce opioid analgesia
- Is ***effective*** in multiple models of OUD
- ➢ **Good candidate for IND-enabling studies and development**



VK4-116 attenuates oxycodone-induced reinstatement of drug seeking

Development of Investigational New Drugs for Clinical Testing

Selective dopamine D3 receptor antagonists for the treatment of OUD



Human D3R complex with D2/D3 antagonist. Chien *et al.*, *Science* (2010)

Goal:

- **Complete preclinical development of a lead D3R antagonist for IND filing and entry into clinical studies**

Current status:

- GMP manufacturing and formulation development
  - ✓ *Streamlined and optimized manufacturing process*
  - ✓ *Overall yield of API increased 20-fold*
- Non-GLP and GLP safety assessments underway
- Development of back-up compound lead series

➢ **Ideal collaboration between research/initial translation with preclinical development expertise and resources at NCATS to push aggressively towards IND**

Collaborations between external OUD/Pain domain experts and NCATS translational experts enabling diverse and rapid progress

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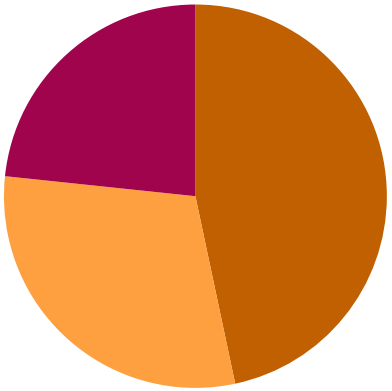
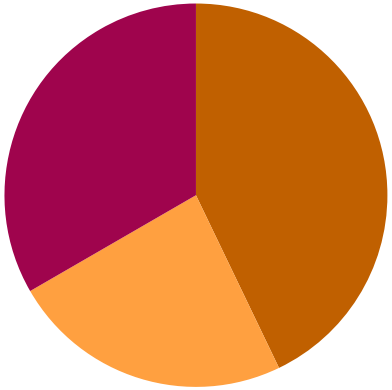
Ongoing Projects

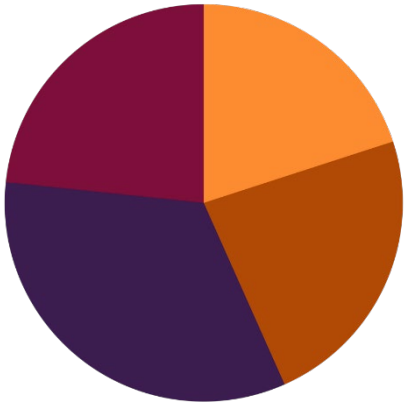
Condition



Applicant Sector



NCATS Component



- IPSC-derived Cells for Pain and Addiction Research
- 3D Biofabricated Tissue Models
- Development of Pharmacological Probes for Novel Targets
- Development of Investigational New Drugs for Clinical Testing

Discussion