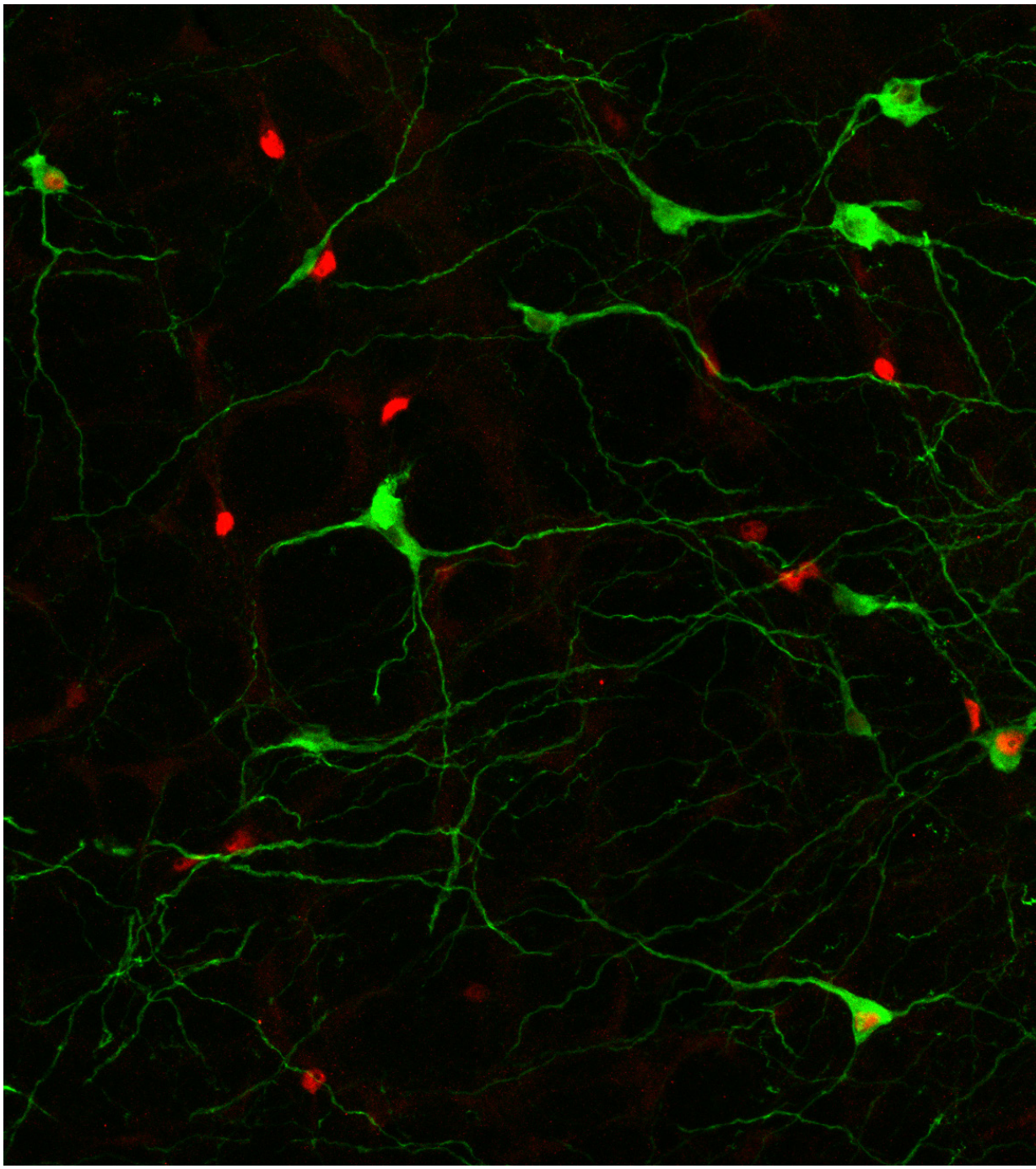
INRC

International Narcotics Research Conference

JULY 22–24
2020 — Valencia ES

Program Book



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Welcome to INRC 2020

Welcome to International Narcotics Research Conference – INRC – conference in 2020!

Thank you for attending our very first online conference. We are very pleased to be able to hold our yearly meeting and welcome you to attend this amazing science content despite the current challenges. This year will honor our fantastic undergraduate, graduate students and postdoctoral researchers and give them the voice they deserve to present their latest results. Let's enjoy some science.

zoom

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⚠ Rules for the Conference:

- **NO RECORDING.** All talks will be recorded and available on our website for a limited amount of time after the conference. It is very important to abide by these rules to encourage open communication and trust within our community.
- Please do not distribute the links to the conference. We are trying our best to avoid being 'zoom-bombed' by not distributing them widely. Anyone who wants to attend can **register here** for $5. If it's an issue of money, please email us at *internationalnarcoticsresearch@gmail.com* and we are happy to provide a code to waive the fee.
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- Keep yourself muted during all talks to limit background noise.
- To ask questions during webinars, please use the "Q&A" function. These questions will be considered by the moderators to ask the speaker. Please use the "Chat" function for any other comments pertaining to the talk.
- Have fun and enjoy the science.

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Recording Restrictions

Presentations will be recorded by the INRC for rebroadcast with permission from presenters and posted on the INRC website with restricted access (password protected) for attendees who can not participate during the live session. Unauthorized recordings by attendees will not be allowed. Prior to quoting or publishing any information presented at a conference in any publication, written or electronic, written approval of the contributing member must first be obtained.

Without previous written consent of the contributing member, the audio or video recording of oral presentations and discussions, the photography/screen-shooting of slides, and printed or electronic quotes from papers, during the conference is strictly prohibited.

These restrictions apply to each attendee and are intended to cover social networks, blogs, tweets or any other publication, distribution, communication or sharing of information presented or discussed at the conference.

Each attendee acknowledges and agrees to these restrictions when registration is accepted and as a condition of being permitted to attend.

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Unauthorized Sharing of Conference Links

Our attendance is limited to license constraints. To ensure that all attendees can access the meeting access to the conference must be limited to paid registration. **Sharing the access links with anyone is thus prohibited.** Individuals must register individually and can ask for a fee waiver if necessary.

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To avoid unwanted disruptions (i.e. "zoom-bombing") attendees should **not share any links to the virtual conference rooms**. Attendees, unless presenting, will turn their microphones/cameras off. Any questions addressed to the speaker should be typed in the chat window. Moderators will select questions within this chat window and share them with the speaker according to the time remaining within the time allotted. Cameras may be on or off depending on personal choice, although keeping your camera on may foster a better experience for the speaker as they deliver their talk to the audience. A virtual background will be shared with the speakers if they decide to use it.

Inappropriate Behavior Policy

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Schedule

Eastern Time	JULY 22 WED	JULY 23 THU	JULY 24 FRI
11:00am			
11:10am	INRC Welcome Reception	Iqira Saeed	Manish K. Madasu
11:20am		Anna Gutridge	Michelle Morochnik
11:30am	Sam Groom	Arryn Blaine	Alexander French
11:40am	Sweta Adhikary	Samuel Singleton	Sarah C. Simmons
11:50am	Jade Degrandmaison	Farhana Sakloth	Susan Ahmedyar
12:00pm	Julia K. Brynildsen	Javier Cuitavi	Dani Cao
12:10pm	Besma Benredjem	Eden Anderson	Moriah L. Jacobson
12:20pm	Zoë Dworsky-Fried	Gregory Grecco	Valentina Martinez Damonte
12:30pm	Sineadh M. Conway	Lani Tieu	Courtney A. Bouchet
12:40pm	Kaitlin C. Reeves	David Reiner	Bryan Sears
12:50pm	Crystal Lemchi	Darrell Eacret	Zachariah Bertels
1:00pm	Devan Gomez	Marwa Mikati	Evan F. Fullerton
1:10pm	Lauren C. Smith	Round Table (1hour) Academic and Industry Career	Benjamin M. Clements
1:20pm	Ethan M. Anderson		Sarah Palumbo
1:30pm	Matthew S. Scarnati		Tamara Markovic
1:40pm	Hannah Frye		Kylie B. McPherson
1:50pm	Shijia Liu		Virtual INRC Closure
2:00pm	Jacob A. Beierle		Valencia Announcement

INRC Welcome | Goodbye, Opioid Signaling, Reward—Addiction, Pain—Analgesia, Kappa, Round Table

INRC Welcome | Goodbye, Opioid Signaling, Reward—Addiction, Pain—Analgesia, Kappa, Round Table

Day 1 • July 22nd

Introduction

11:00am – 11:20am

Larry Toll

Talks session #1

11:20am – 12:30pm

Opioid Signaling

Moderators:

Larry Toll

Meritxell Canals

Speakers:

11:20am – 11:30am

Sam Groom

A novel G protein-biased agonist at the μ opioid receptor induces substantial receptor desensitization through GRK

11:30am – 11:40am

Sweta Adhikary

Mu opioid receptors regulate adenosine tone in stratal Synapses

11:40am – 11:50am

Jade Degrandmaison

In vivo mapping of the delta-opioid receptor interactome using knock-in mice

11:50am – 12:00pm

Julia K. Brynildsen

Gene coexpression patterns predict opiate-induced brain state transitions

12:00pm – 12:10pm

Besma Benredjem

In vitro signaling profiles of opioid ligands allow to infer their clinical responses

12:10pm – 12:20pm

Zoë Dworsky-Fried

Central amygdala inflammation drives pain hypersensitivity and impaired opioid signalling in a mouse model of multiple sclerosis

12:20pm – 12:30pm

Sineadh M. Conway

Developing a novel approach for in vivo electrochemical detection of opioid peptides

Talk session #2

12:30pm – 2:00pm

Reward – Addiction

Moderators:

Emily Jutkiewicz

Jose Moron-Concepcion

Speakers:

12:30pm – 12:40pm

Kaitlin C. Reeves

Mu opioid receptors on vGluT2-expressing glutamatergic neurons modulate opioid reward

12:40pm – 12:50pm

Crystal Lemchi

Development of a Novel Neonatal Opioid Exposure Model in Mice

12:50pm – 1:00pm

Devan Gomez

Mesolimbic subcicruit-specific adaptations following protracted morphine withdrawal and altered motivated behavior

1:00pm – 1:10pm

Lauren C. Smith

Validation of a nicotine vapor self-administration model in rats with relevance to electronic cigarette use

1:10pm – 1:20pm

Ethan M. Anderson

HDAC5 in the rat nucleus accumbens suppresses cued and drug-primed reinstatement of heroin seeking in a D1 vs D2 cell type-specific manner

1:20pm – 1:30pm

Matthew S. Scarnati

Differential sensitivity of human neurons carrying μ opioid receptor (MOR) N40D variants in response to ethanol

1:30pm – 1:40pm

Hannah Frye

Sex Differences in the Role of Cornichon Homolog-3 on Opioid Use Disorder Risk and Spatial Memory

1:40pm – 1:50pm

Shijia Liu

Neural basis of opioid-induced respiratory depression and its rescue

1:50pm – 2:00pm

Jacob A. Beierle

Differences in oxycodone state dependent learning between nearly isogenic BALB/cJ and BALB/cByJ mouse substrains map to chromosomes 14 and 6

Sam Groom
Ph.D. Student

Sam Groom*, Nina Kathleen Blum, Alex Conibear, Alex Disney, Stephen Husbands, Yangmei Li, Lawrence Toll, Stefan Schluz, Graeme Henderson, Eamonn Kelly, Chris Bailey

A novel G protein-biased agonist at the μ opioid receptor induces substantial receptor desensitization through GRK

My recent work has determined that the cyclic endomorphin analogue Tyr-c[D-Lys-Phe-Tyr-Gly] (Compound 1) is a novel G protein-biased agonist at the μ opioid receptor. Surprisingly, we found that Compound 1 induces considerable desensitization of the μ opioid receptor in rat locus coeruleus neurons. Compound 1-induced receptor desensitization occurred through GRK in spite of its G protein-biased pharmacology. Our findings cast doubt on the assumption that G protein-biased agonists will categorically evade receptor desensitization and tolerance.

Day 1 • July 22nd
Session #1, Talk #1
Opioid Signaling

11:20am – 11:30am

Sweta Adhikary
Graduate Student

Sweta Adhikary*, John T. Williams, & William T. Birdsong

Mu opioid receptors regulate adenosine tone in stratal Synapses

Activation of mu opioid receptors inhibits adenosine tone in striatal synapses through a cAMP mediated pathway. Selectively knocking-out mu opioid receptors from pre or post synaptic compartments does not augment adenosine tone in the presence of morphine, but a global mu knock out does. Additionally, adenosine is regulated by postsynaptic medium spiny neurons in the striatum.

Day 1 • July 22nd
Session #1, Talk #2
Opioid Signaling

11:30am – 11:40am

Jade Degrandmaison
Ph.D. Candidate

Jade Degrandmaison*, Khaled Abdallah, Véronique Blais, Samuel Génier, Marie-Pier Lalumière, Francis Bergeron, Catherine M. Cahill, Jim Boulter, Christine L. Lavoie, Jean-Luc Parent and Louis Gendron

In vivo mapping of the delta-opioid receptor interactome using knock-in mice

Despite its significant potential as a therapeutic target for chronic pain management, our understanding of the molecular and cellular mechanisms regulating the trafficking and signaling of the delta-opioid receptor (DOPr) remains fragmentary. Using brain homogenates from our newly generated FLAG-DOPr-KO (knock-out) and FLAG-DOPr-KI (knock-in) mouse models, we identified several novel endogenous DOPr interactors involved in protein folding, trafficking, and signal transduction, as well as other proteins belonging to the receptors/channels/transporters family. We also describe the generation of a conditional KI FLAG-DOPr mouse line, an invaluable tool to investigate DOPr functions in specific neuron populations and circuits.

Day 1 • July 22nd
Session #1, Talk #3
Opioid Signaling

11:40am – 11:50am

Julia K. Brynildsen
Ph.D. Candidate

Julia K. Brynildsen*, Kyla D. Mace, Eli J. Cornblath, Carmen Weidler, Fabio Pasqualetti, Danielle S. Bassett, and Julie A. Blen

Gene coexpression patterns predict opiate-induced brain state transitions

Reconfiguration of neuronal connectivity may explain heightened opioid abuse liability in individuals with a history of chronic drug exposure. To characterize network-level changes in neuronal activity induced by chronic opiate exposure, we constructed network models from FOS expression data in mice that are morphine-naïve, morphine-dependent, or have undergone 4 weeks of withdrawal from chronic morphine exposure. We demonstrate that basal gene expression patterns are predictive of changes in FOS correlation networks in the morphine-dependent state and identify key brain regions that are particularly influential in driving transitions between opiate-naïve and opiate-dependent brain states.

Day 1 • July 22nd
Session #1, Talk #4
Opioid Signaling

11:50am – 12:00pm

Besma Benredjem

Ph.D. Student

Besma Benredjem*, Jonathan Gallion, Dennis Pelletier, Paul Dallaire, Johanie Charbonneau, Darren Cawkill, Karim Nagi, Mark Gosink, Viktoryia Lukashova, Stephen Jenkinson, Yong Ren, Christopher Somps, Brigitte Murat, Emma Van Der Westhuizen, Christian Le Gouill, Olivier Lichtarge, Anne Schmidt, Michel Bouvier, Graciela Pineyro

In vitro signaling profiles of opioid ligands allow to infer their clinical responses

We have developed a method that uses preclinical responses of well-known prescription opioids and of novel molecules to classify them according to similarities in their signaling profiles. We have found that the categories that result from this classification are associated with different degrees of clinically reported side effects (such as respiratory depression). This method could help to identify better drug candidates, allowing to advance to clinical testing only those with less side effects potential.

Day 1 • July 22nd
Session #1, Talk #5
Opioid Signaling

12:00pm – 12:10pm

Zoë Dworsky-Fried

M.S.c Student

Zoë Dworsky-Fried*, Bradley J Kerr, Anna MW Taylor

Central amygdala inflammation drives pain hypersensitivity and impaired opioid signalling in a mouse model of multiple sclerosis

Chronic pain is one of the most frequent and debilitating symptoms associated with the autoimmune disorder multiple sclerosis (MS). In this study, we use a mouse model of MS to show that inflammation within the central amygdala alters anti-nociceptive signalling leading to blunted opioid analgesia. Our data identify a novel mechanism for impaired pain control in autoimmune disorders and highlight potential strategies, such as targeting inflammation, to improve analgesic efficacy in MS.

Day 1 • July 22nd
Session #1, Talk #6
Opioid Signaling

12:10pm – 12:20pm

Sineadh M. Conway
Postdoctoral Researcher

Sineadh M. Conway*, Graydon B. Gereau, Loc V. Thang, John R. Cirrito, Carla M. Yuede, Ream Al-Hasani

Developing a novel approach for in vivo electrochemical detection of opioid peptides

The endogenous opioid peptide systems are critical for analgesia, reward processing, and negative affect, however research on their in vivo function in modulation of these behaviors has been challenging due to an inability to reliably and consistently detect dynamic changes in opioid peptides. To fill this gap, we have developed microimmunoelectrodes (MIEs) for rapid and sensitive detection of opioid peptides. Using square wave voltammetry, we show that dynorphin antibody-coated MIEs are sensitive and selective to increasing concentrations of dynorphin in the fmol range, and we are currently working to demonstrate the utility of these MIEs both in vitro via brain slice preparation and in vivo for real-time, rapid detection of endogenous opioid peptide release in awake and behaving animals.

Day 1 • July 22nd
Session #1, Talk #7
Opioid Signaling

12:20pm – 12:30pm

Kaitlin C. Reeves
Ph.D. Candidate

Kaitlin C. Reeves*, Megan J. Kube, Gregory G. Grecco, Brandon M. Fritz, Braulio Muñoz, Fuqin Yin, Yong Gao, David L. Haggerty, Hunter J. Hoffman, Brady K. Atwood

Mu opioid receptors on vGluT2-expressing glutamatergic neurons modulate opioid reward

The role of mu opioid receptor (MOR)-mediated regulation of GABA transmission in opioid reward is well established, but much less is known about MOR-mediated regulation of glutamate transmission and how this relates to drug reward; therefore, we created a transgenic mouse that lacks MORs in vGluT2-expressing neurons (MORflox-vGluT2cre). Compared to wild-type littermate controls, these MORflox-vGluT2cre mice have disrupted opioid reward, consume less oxycodone, lack oxycodone-induced locomotor stimulation, and display baseline withdrawal-like responses following the development of oxycodone dependence. However, other MOR-mediated behaviors, including oxycodone-induced analgesia, are unaffected, suggesting that MOR-mediated regulation of glutamate transmission plays a specific role in opioid reward and withdrawal.

Day 1 • July 22nd
Session #2, Talk #1
Reward – Addiction

12:30pm – 12:40pm

Crystal Lemchi

Ph.D. Candidate

Crystal Lemchi*, Amelia Dunn, Juliet Mengaziol, Shivon Robinson and Julie A. Blendy

Development of a Novel Neonatal Opioid Exposure Model in Mice

The long-term effects of chronic opioid exposure during early life are not well characterized due to many confounding factors in human studies and lack of consistency in animal models. Our lab has created a novel mouse model of opioid exposure [spanning both in utero and PND 1-14], which encompasses the human equivalent of “three-trimester” opioid exposure and recapitulates characteristic phenotypes associated with NOWS during both development and withdrawal. Despite this robust withdrawal, preliminary results suggest few long-term behavioral consequences (CPP, LH,TST) of this NOWS model.

Day 1 • July 22nd
Session #2, Talk #2
Reward – Addiction

12:40pm – 12:50pm

Devan Gomez

Graduate Student

Devan Gomez*, Matthew Hearing

Mesolimbic subcircuit-specific adaptations following protracted morphine withdrawal and altered motivated behavior

Our lab has found that protracted withdrawal from a dependence-inducing regimen of morphine reduces excitation and increases GABAAR-mediated inhibition within a subpopulation of lateral VTA dopamine neurons projecting to the lateral NAc shell. These adaptations align with preliminary findings suggesting that prior induction of dependence increases subsequent motivation for intravenously available morphine at this protracted withdrawal time point. These data underscore the significance of distinguishing functional differences between dopaminergic circuitry and their potential to separately contribute to neurobehavioral alterations related to opioid withdrawal, relapse and shifts in motivated states that drive drug-seeking.

Day 1 • July 22nd
Session #2, Talk #3
Reward – Addiction

12:50pm – 1:00pm

Lauren C. Smith

Graduate Student

Lauren C. Smith*, Marsida Kallupi, Lani Tieu, Kokila Shankar, Abigail Jaquish, Jamie Barr, Yujuan Su, Nathan Velarde, Sharona Sedighim, Lieselot L. G. Carrette, Mike Klodnicki, Xin Sun, Giordano de Guglielmo, Olivier George

Validation of a nicotine vapor self-administration model in rats with relevance to electronic cigarette use

There is currently no rodent model of nicotine vapor self-administration, so we developed a novel model of voluntary electronic cigarette use in rats using operant behavior. We found that rats voluntarily exposed themselves to nicotine vapor to the point of reaching blood nicotine levels that are similar to humans. Moreover, nicotine vapor self-administration resulted in addiction-like behaviors, including somatic signs of withdrawal, allodynia, anxiety-like behavior, and relapse-like behavior after 3 weeks of abstinence. These findings validate a novel animal model of nicotine vapor self-administration in rodents with relevance to electronic cigarette use in humans and demonstrate the addictive properties and harmful effects of chronic nicotine vapor self-administration.

Day 1 • July 22nd
Session #2, Talk #4
Reward – Addiction

1:00pm – 1:10pm

Ethan M. Anderson

Research Assistant Professor

Ethan M. Anderson*, Evgeny Tsvetkov, Allison Galante, Makoto Taniguchi, and Christopher W. Cowan

HDAC5 in the rat nucleus accumbens suppresses cued and drug-primed reinstatement of heroin seeking in a D1 vs D2 cell type-specific manner

Histone deacetylase 5 (HDAC5) is an epigenetic regulator that shuttles between the nucleus and cytoplasm following drug exposure and alters intrinsic excitability of medium spiny neurons (MSNs) in the nucleus accumbens (NAc). Here, using overexpression and knockdown manipulations of HDAC5 in the rat NAc, I show bi-directional effects of HDAC5 on 3 types of heroin-seeking behavior following several weeks of heroin self-administration. Finally, I show that overexpression of HDAC5 reduces cue-induced reinstatement when selectively expressed in D1-MSNs and this same HDAC5 overexpression in D2-MSNs reduces heroin-primed reinstatement selectively; importantly, these results suggest that the current dogma concerning opposing roles of D1 vs D2-MSNs on drug-seeking behavior may be incomplete and these separable MSNs may instead have complimentary roles in drug-seeking behavior.

Day 1 • July 22nd
Session #2, Talk #5
Reward – Addiction

1:10pm – 1:20pm

Matthew S. Scarnati
Postdoctoral Researcher

Matthew S. Scarnati*, Andrew J.,Boreland, Marisa Joel, Ronald P. Hart, Zhiping P. Pang

Differential sensitivity of human neurons carrying μ opioid receptor (MOR) N40D variants in response to ethanol

There is a limited understanding of the precise cellular and molecular mechanisms underlying AUD in humans. A functional polymorphism of the mu-opioid receptor (MOR) N40D may alter the risk of developing AUD. iPS and induced neuronal (iN) cell technology provide unique opportunities to model AUD in a human context. Alcohol application reveals that the MOR genotype confers differential sensitivity to synaptic output which depends on ethanol exposure time and concentration for AD-iNs and may help explain alcohol dependence in individuals who carry the MOR D40 SNP.

Day 1 • July 22nd
Session #2, Talk #6
Reward – Addiction

1:20pm – 1:30pm

Hannah Frye
Graduate Student

Hannah E. Frye*, Yukitoshi Izumi, Min-Yu Sun, Sidney B. Williams, Christopher R. Trousdale, Alexis N. Harris, Andrew D. Sauerbeck, Terrance T. Kummer, Steven Mennerick, Charles F. Zorumski, Elliot C. Nelson, Joseph D. Dougherty, Jose A. Morón

Sex Differences in the Role of Cornichon Homolog-3 on Opioid Use Disorder Risk and Spatial Memory

Single nucleotide polymorphisms (SNPs) in CNIH3, the gene which encodes for the AMPA receptor (AMPAR) auxiliary protein cornichon homolog-3 (CNIH3), are correlated with reduced risk of opioid use disorder in humans. New data suggest this correlation is stronger in women, and in mouse studies CNIH3 only affects spatial memory, hippocampal synaptic plasticity, and synaptic density in females during the metestrus stage of the estrous cycle. Our study defines a sex-specific role for CNIH3 in spatial memory formation and synaptic plasticity, which are highly involved in opioid use disorder and relapse.

Day 1 • July 22nd
Session #2, Talk #7
Reward – Addiction

1:30pm – 1:40pm

Shijia Liu
Ph.D. Candidate

Shijia Liu*, Dongil Kim, Tae Gyu Oh, Gerald Pao, Jonghyun Kim, Richard D. Palmiter, Ronald M. Evans, Sung Han.

Neural basis of opioid-induced respiratory depression and its rescue

Opioid-induced respiratory depression (OIRD) is the direct cause of the rapidly evolving opioid crisis, yet its underlying neurobiological mechanisms are not well understood. We identify that a genetically defined neuronal population in the lateral parabrachial nucleus expressing μ-opioid receptors (PBL^{Oprm1} neurons) are involved in regulating breathing rhythm and OIRD pathogenesis. In addition, we find that activating PBL^{Oprm1} neurons via artificial and endogenous G-protein coupled receptor signaling pathways rescues OIRD, thereby providing insights on novel therapeutic interventions of OIRD in humans.

Day 1 • July 22nd
Session #2, Talk #8
Reward – Addiction

1:40pm – 1:50pm

Jacob A. Beierle
Graduate Student

Jacob A. Beierle*, Emily Yao, Julia Scotellaro, Gary Peltz, Camron D. Bryant

Differences in oxycodone state dependent learning between nearly isogenic BALB/cJ and BALB/cByJ mouse substrains map to chromosomes 14 and 6

Variation in subjective sensitivity to the rewarding effects of opioids is heritable and can influence addiction liability. In inbred BALB/c substrains we identified robust differences in state-dependent retrieval of oxycodone conditioned reward, but not drug-free reward as measured via conditioned place preference. Because these substrains are over 99% isogenic, identification of the genetic factors influencing this trait is greatly facilitated compared to traditional F2 crosses. I will discuss identification of 2 major-effect QTLs influencing state dependent learning/retrieval of oxycodone reward on proximal chromosome 14, and a female specific locus on chromosome 6 as well as the limited number of candidate genes that lie underneath these loci.

Day 1 • July 22nd
Session #2, Talk #9
Reward – Addiction

1:50pm – 2:00pm

• Back to schedule

Day 2 • July 23rd

Talks session #3

11:00am – 11:50am

Pain – Analgesia

Moderators:

Gregory Corder
Tuan Trang

Speakers:

11:00am – 11:10am

Iqira Saeed

Can opioid exposure alter cancer incidence?

11:10am – 11:20am

Anna Gutridge

Pharmacological Characterization of Natural and Synthetic Akuamma Alkaloids for Pain Therapeutics

11:20am – 11:30am

Arryn Blaine

Investigating the Cellular and Behavioral Effects of δ-Opioid Receptor Mediated β-arrestin 1 Signaling

11:30am – 11:40am

Samuel Singleton

TRV130 partial agonism and capacity to produce analgesic tolerance revealed through reducing available mu opioid receptor number

11:40am – 11:50am

Farhana Sakloth

In Vivo Evidence that Positive Allosteric Modulators of the μ-Opioid Receptor Enhance the Antinociceptive Efficacy of Clinically Used Opioids, but not the Adverse Effects Associated with their Repeated Administration

Talks session #4

11:50am – 1:00pm

Reward – Addiction

Moderators:

Thomas Kash
Lucia Hipolito

Speakers:

11:50am – 12:00pm

Javier Cuitavi

Microglia-mediated Mu Opioid Receptor alterations? A new insight into pain-induced alcohol relapse in female rats

12:00pm – 12:10pm

Eden Anderson

Opioid self-administration induced sex-specific medial prefrontal cortex plasticity and deficits in cognitive flexibility

12:10pm – 12:20pm

Gregory Grecco

Prenatal Methadone Exposure Disrupts Neurobehavioral Development

12:20pm – 12:30pm

Lani Tieu

Identification of Individual Differences in Response to Methadone, Buprenorphine, and Naltrexone in an Animal Model of Opioid Use Disorder

12:30pm – 12:40pm

David Reiner

Role of projections between piriform and orbitofrontal cortex in relapse to fentanyl seeking after food choice-induced voluntary abstinence

12:40pm – 12:50pm

Darrell Eacret

Investigations into the behavioral and molecular consequences of chronic opioids and the relationship to disrupted sleep

12:50pm – 1:00pm

Marwa Mikati

In vivo detection of endogenous opioid peptides and their role in opioid withdrawal syndrome

Round Table

1:00pm – 2:00pm

Moderators:

Andrea Bedini

Assistant professor, University of Bologna

Lucia Hipolito

Associate professor, University of Valencia

Ream Al-Hasani

Assistant professor, St Louis College of Pharmacy

Jose Moron-Concepcion

Professor, Washington University in St. Louis

Amynah Pradhan

Associate Professor, University of Illinois in Chicago

John Streicher

Assistant professor, University of Arizona

Katherine Martucci

Assistant professor, Duke University

Iqira Saeed
Ph.D. Student

Can opioid exposure alter cancer incidence?

There is considerable controversy regarding whether opioids influence cancer-related outcomes in patients with pre-existing cancer. Less work has explored whether opioid exposure increases the risk of cancer-related outcomes in opioid users who were initially free from cancer. We report a systematic review which examines the relationship between opioid exposure and cancer outcomes in populations of individuals who were cancer-free prior to opioid exposure.

Day 2 • July 23rd
Session #3, Talk #1
Pain – Analgesia

11:00am – 11:10am

Anna Gutridge
Graduate Student

Gutridge AM*, Hennessy MR, Argade MD, Rhoda ES, Royer QH, Riley AP, van Rijn RM

Pharmacological Characterization of Natural and Synthetic Akuamma Alkaloids for Pain Therapeutics

Picralima nitida, commonly known as akuamma, is a tree that produces opioidergic alkaloids (Menzies et al., Eur. J. Pharmacol.1998) and is used most generally for its analgesic and anti-inflammatory properties (Erharuyi et al., Asian Pac. J. Trop. Med. 2014). Due to their ability to agonize the μ-opioid receptor (Menzies et al., Eur. J. Pharmacol. 1998), I hypothesized these alkaloids can be used in the treatment of pain. Six akuamma alkaloids were pharmacologically characterized at the μ-, δ- and κ- opioid receptors (μOR, δOR, κOR) for binding affinity and biased signaling activity, and the compounds with the highest μOR potency were then tested for analgesic properties in nociception paradigms.

Day 2 • July 23rd
Session #3, Talk #2
Pain – Analgesia

11:10am – 11:20am

Arryn Blaine
Graduate Student

Arryn Blaine*, Dr. Richard van Rijn, Rebecca Liu

Investigating the Cellular and Behavioral Effects of δ-Opioid Receptor Mediated β-arrestin 1 Signaling

Opioids targeting the delta opioid receptor have been investigated as alternative analgesic strategy to avoid adverse effects observed with mu opioids. Unfortunately, delta opioids have a tendency to induce seizures, a severe side effect linked to arrestin signaling. Here I investigated seizure severity and ERK signaling by delta opioids with different arrestin efficacy in male and female wild-type, beta-arrestin 1 and beta-arrestin 2 KO mice.

Day 2 • July 23rd
Session #3, Talk #3
Pain – Analgesia

11:20am – 11:30am

Samuel Singleton
Ph.D. Student

Samuel Singleton*, Daniel Baptista-Hon, Emily Edelston, Kirsty McCaughey, Ewan Camplisson, Tim G Hales

TRV130 partial agonism and capacity to produce analgesic tolerance revealed through reducing available mu opioid receptor number

The possibility that β-arrestin2 recruitment to mu receptors may contribute to opioid side effects led to the development of TRV130, a biased agonist in favour of G-protein signalling. However, apparent bias may be confounded by receptor overexpression. We examined the efficacies and apparent potencies of mu agonists with full and partial receptor availability following exposure to the irreversible mu antagonist β-FNA. In vivo, we also assessed whether receptor number influenced the development of analgesic tolerance using heterozygous mice expressing 50% fewer mu receptors. TRV130 was a very weak partial agonist in vitro even without prior exposure to β-FNA. TRV130 was highly potent and caused no analgesic tolerance in wild type mice. In heterozygous mice, TRV130 was equally efficacious but caused profound tolerance after only 4 days. These findings emphasise the need for consideration of receptor reserve when characterising new opioid agonists. Furthermore, they suggest the beneficial side effect profile of reportedly biased agonists may be a result of partial agonism.

Day 2 • July 23rd
Session #3, Talk #4
Pain – Analgesia

11:30am – 11:40am

Farhana Sakloth

Postdoctoral Researcher

Farhana Sakloth*, Kerri Pryce, Hye Jin Kang, Abhijeet Kapoor, Tao Che, Lihuai Qin, Feodora Bertherat, H. Ümit Kaniskan, Jian Jin, Bryan Roth, Venetia Zachariou, and Marta Filizola

In Vivo Evidence that Positive Allosteric Modulators of the μ-Opioid Receptor Enhance the Antinociceptive Efficacy of Clinically Used Opioids, but not the Adverse Effects Associated with their Repeated Administration

We report two small molecules from a chemical series of Positive allosteric modulators (PAMs) of the μ-opioid receptor (MOR) exhibiting: (a) opposite biased signaling in vitro; (b) a differential enhancement of the antinociceptive efficacy of oxycodone, morphine, and methadone in mouse models of pain, and (c) a lack of potentiation of an unwanted side effect resulting from excessive opioid administration. This series of MOR PAMs holds promise for the development of adjuncts to opioid therapy to mitigate against overdose and opioid use disorders.

Day 2 • July 23rd
Session #3, Talk #5
Pain – Analgesia

11:40am – 11:50am

Javier Cuitavi

Ph.D. Student

Javier Cuitavi*, Jesús David Lorente, Yolanda Campos-Jurado, Natalia Landsberg and Lucía Hipólito

Microglia-mediated Mu Opioid Receptor alterations? A new insight into pain-induced alcohol relapse in female rats

Microglia play a role in pain and addictive processes and proinflammatory cytokines regulate Mu Opioid Receptor (MOR) expression. We show how microglial activation, neuroinflammation and MORs levels variates during the abstinence and the relapse phases in female rats and we assess the role that pain plays on it.

Day 2 • July 23rd
Session #4, Talk #1
Reward – Addiction

11:50am – 12:00pm

Eden Anderson
Postdoctoral Researcher

Eden Anderson*, Annabel Engelhardt, Skyler Demis, Elissa Porath, Matthew Hearing

Opioid self-administration induced sex-specific medial prefrontal cortex plasticity and deficits in cognitive flexibility

Women transition to addiction faster and experience greater difficulties remaining abstinent, however what drives this is unknown. We show that self-administration of the opioid, remifentanil, causes a long-lasting decrease in ex vivo excitability but augments firing capacity of pyramidal neurons in the prelimbic cortex of mice. This phenomenon occurs faster in females, manifests from sex-specific changes in excitatory and inhibitory synaptic regulation and aligns with a significant impairment in cognitive flexibility that can be induced and rescued using chemogenetic manipulations.

Day 2 • July 23rd
Session #4, Talk #2
Reward – Addiction

12:00pm – 12:10pm

Gregory Grecco
M.D-Ph.D. Student

Gregory G. Grecco*, Briana Mork, David L. Haggerty, Kaitlin C. Reeves, Yong Gao, Hunter Hoffman, Andrea R. Masters, Bryan K. Yamamoto, Patrick L. Sheets, Brady K. Atwood.

Prenatal Methadone Exposure Disrupts Neurobehavioral Development

We have recently developed and characterized a translational mouse model of prenatal methadone exposure (PME) that resembles the typical pattern of opioid use in a pregnant woman who is first dependent on oxycodone prior to gestation, then enters a methadone maintenance therapy program, and subsequently becomes pregnant while maintained on methadone. Using this model, the impact of PME on behavioral development and neuronal properties using brain slice electrophysiological measures was investigated in offspring. Methadone was found to accumulate in the fetal compartment relative to maternal concentrations. In addition to high methadone concentrations in the fetal brain, PME produces substantial impairments in behavioral development specifically in sensorimotor and locomotor performance which was associated with alterations in motor cortical neuron intrinsic properties and synaptic connectivity.

Day 2 • July 23rd
Session #4, Talk #3
Reward – Addiction

12:10pm – 12:20pm

Lani Tieu
Research Assistant

Lani Tieu*, Lauren Smith, Giordano de Guglielmo, Marsida Kallupi, Olivier George

Identification of Individual Differences in Response to Methadone, Buprenorphine, and Naltrexone in an Animal Model of Opioid Use Disorder

The current medications for opioid use disorder (buprenorphine, methadone, and naltrexone) significantly reduce craving but there are substantial individual differences in response to these treatments, and the reason for such difference is poorly known. Here, we tested the hypothesis that similar individual differences may be observed in a large population of heterogeneous stock rats, that have been bred to maximize genetic diversity, using a behavioral paradigm relevant to opioid use disorder. We found that ~65% of rats decreased their motivation to take oxycodone with at least one treatment and observed large individual difference for each treatment. To unveil the genetic, cellular, and molecular basis of these differences, we created the Oxycodone Biobank (*www.oxycodonebiobank.org*), from which investigators can request biological samples, including blood, urine, feces, brain, liver, kidney, and other organs.

Day 2 • July 23rd
Session #4, Talk #4
Reward – Addiction

12:20pm – 12:30pm

David Reiner
Postdoctoral Researcher

David J Reiner*, Olivia M Lofaro, Sarah V Applebey, Hannah Korah, Marco Venniro, Carlo Cifani, Jennifer M Bossert, Yavin Shaham

Role of projections between piriform and orbitofrontal cortex in relapse to fentanyl seeking after food choice-induced voluntary abstinence

There are few preclinical studies of fentanyl relapse, and these studies have used experimenter-imposed (forced) abstinence procedures, despite that in humans, abstinence is often voluntary, with drug available in the drug environment but forgone in favor of non-drug alternative rewards. Using immunohistochemistry, anatomical tracing, and classical pharmacology, I identified a critical role of projections between piriform and orbitofrontal cortices in relapse to fentanyl seeking after food choice-induced voluntary abstinence in both male and female rats. These data revealed a surprising finding, that the piriform cortex which is traditionally thought of as an olfaction-related region and not previously studied in the context of drug reinstatement/relapse, is critical for relapse to fentanyl seeking.

Day 2 • July 23rd
Session #4, Talk #5
Reward – Addiction

12:30pm – 12:40pm

Darrell Eacret

Research Assistant

Darrell Eacret*, Polina Fenik, Guanxia Zhan, Sigrid C. Veasey, and Julie A. Blendy

Investigations into the behavioral and molecular consequences of chronic opioids and the relationship to disrupted sleep

Disrupted sleep is a side effect of opioid use and withdrawal. We used an oral morphine administration paradigm and found significant alterations in sleep parameters during morphine exposure and withdrawal. Increases in wakefulness during morphine accompanied a cortical gene expression profile that is reminiscent of an inflammatory sleep deprivation state. Ongoing studies are focused on identifying molecular mechanisms underlying these changes and how to intervene with treatments during withdrawal to improve sleep disturbances and reduce withdrawal symptoms.

Day 2 • July 23rd
Session #4, Talk #6
Reward – Addiction
12:40pm – 12:50pm

Marwa Mikati

Ph.D. Candidate

Marwa Mikati*, Kia Barclay, Petra Erdmann-Gilmore, Robert Sprung, Reid Townsend, Ream Al-Hasani

In vivo detection of endogenous opioid peptides and their role in opioid withdrawal syndrome

The withdrawal syndrome associated with abstinence from opioids often results in relapse, is sometimes fatal and prevents long-term abstinence. Studies have shown that increased expression of dynorphin mRNA, the endogenous kappa opioid receptor ligand, increases in the nucleus accumbens during withdrawal. However, there is not a reliable method to directly measure in vivo changes in opioid peptides. Here, we propose a novel mouse model of precipitated withdrawal from chronic fentanyl exposure. We also describe a method coupling microdialysis and nano-liquid chromatography/mass spectrometry to allow detection of endogenous opioid peptides in vivo.

Day 2 • July 23rd
Session #4, Talk #7
Reward – Addiction
12:50pm – 1:00pm

Round Table

Academic and Industry Career

Moderators:

Andrea Bedini
Assistant professor, University of Bologna

Lucia Hipolito
Associate professor, University of Valencia

Ream Al-Hasani
Assistant professor, St Louis College of Pharmacy

Jose Moron-Concepcion
Professor, Washington University in St. Louis

Amynah Pradhan
Associate Professor, University of Illinois in Chicago

John Streicher
Assistant professor, University of Arizona

Katherine Martucci
Assistant professor, Duke University

Day 2 • July 23rd
–
Round Table

1:00pm – 2:00pm

Day 3 • July 24th

Talks Session #5

11:00am – 12:20pm

Kappa

Moderators:

Ream Al-Hasani
Lee-Yuan Liu-Chen

Speakers:

11:00am – 11:10am

Manish K. Madasu

Activation of kappa opioid receptor potentiates cold sensation

11:10am – 11:20am

Michelle Morochnick

Modulation of cocaine administration by kappa agonists: nalfurafine and novel pyranopiperazines

11:20am – 11:30am

Alexander French

Effects of biased agonism at the kappa opioid receptor on alcohol consumption in mice

11:30am – 11:40am

Sarah C. Simmons

Early life stress dysregulates kappa opioid receptor signaling within the lateral habenula

11:40am – 11:50am

Susan Ahmedyar

The role of dynorphin/kappa-opioid receptor (DYN-KOR) system in stress-mediated affective disorders and alcohol self-administration in mice

11:50am – 12:00pm

Danni Cao

Characterization of knockin mice harboring kappa opioid receptors (KOR)-inducible Cre recombinase (KOR-iCre), a better tool for precise localization of KOR-expressing neurons

12:00pm – 12:10pm

Moriah L. Jacobson

Kappa Opioid Receptor Desensitization is Required for the Protracted Antidepressant Effects of Ketamine

12:10pm – 12:20pm

Valentina Martinez Damonte

kORs in the VTA modulate GABAergic synaptic plasticity

Talks Session #6

12:20pm – 1:40pm

Pain

Moderators:

Catherine Cahill
Nicolas Massaly

Speakers:

12:20pm – 12:30pm

Courtney A. Bouchet

Differential effects of persistent inflammation on the presynaptic opioid and cannabinoid receptors within the ventrolateral periaqueductal gray

12:30pm – 12:40pm

Bryan Sears

Potential Involvement of Peripheral Opioid Receptors In The Development Of Tolerance To Morphine

12:40pm – 12:50pm

Zachariah Bertels

A translationally significant model of migraine facilitation through chronic morphine is attenuated by PAC1 receptor antagonism

12:50pm – 1:00pm

Evan F. Fullerton

The impact of advanced age on Mu Opioid Receptor signaling in the midbrain periaqueductal gray: implications on analgesia

1:00pm – 1:10pm

Benjamin M. Clements

Influence of Strategically Substituted Agmatines on Opioid-Induced Neuroplasticity

1:10pm – 1:20pm

Sarah Palumbo

Assessment of probable opioid use disorder using electronic health record documentation

1:20pm – 1:30pm

Tamara Markovic

Pain induces somatic adaptations in Ventral Tegmental Area Dopamine neurons to drive anhedonia-like behavior

1:30pm – 1:40pm

Kylie B. McPherson

Changes in intrinsic properties of vlPAG neuron subtype after persistent inflammatory pain

Conclusion and Valencia Meeting presentation

1:40pm – 2:00pm

Speakers :

Larry Toll
Nicolas Massaly
Lucia Hipolito

Manish K. Madasu

Postdoctoral Researcher

Manish K. Madasu*, Loc V. Thang, Priyanka Chilukuri, Sasha Singh, Tayler D. Sheahan, Jordan G. McCall, Ream Al-Hasani

Activation of kappa opioid receptor potentiates cold sensation

Noxious cold sensation is commonly associated with peripheral neuropathies, however there has been limited progress in understanding the mechanism of cold pain. Here we investigate the role of kappa opioid receptor (KOR) in mediating cold sensation. Wildtype mice (WT) injected with U50,488 (U50) (KOR agonist, 5mg/kg i.p) show significant potentiation in the number of jumps on the cold plate compared to controls at 3°C and NorBNI (KOR antagonist) blocked the U50-induced nocifensive responses. Peripheral novel agonist CR845 had a similar effect to U50 on the cold plate. U50 or CR845 had no effect on rectal body temperature vs control, suggesting no role of central thermoregulation. Together, these findings identify a novel role for the peripheral kappa opioid receptor system in the potentiation of cold sensation.

Day 3 • July 24th
Session #5, Talk #1
Kappa

11:00am – 11:10am

Michelle Morochnik

Research Assistant

Michelle Morochnik*, Kyle Windisch, Amelia Dunn, Philip Pikus, Ariel Ben-Ezra, Brian Reed, Mary Jeanne Kreek

Modulation of cocaine administration by kappa agonists: nalfurafine and novel pyranopiperazines

In progressive ratio studies in C57BL/6 mice nalfurafine causes an increase in progressive ratio breakpoint during cocaine self-administration. In two novel kappa opioid receptor agonists, we found one had no effect and the other had a trend toward reduction of progressive ratio breakpoint.

Day 3 • July 24th
Session #5, Talk #2
Kappa

11:10am – 11:20am

Alexander French
Postdoctoral Researcher

Alexander R. French*, Q. Hawk Royer, Anna M. Gutridge and Richard M. van Rijn

Effects of biased agonism at the kappa opioid receptor on alcohol consumption in mice

The roles of kappa opioid receptor (KOR) signaling in regulating stress and reward make it an attractive target for treating alcohol use disorder (AUD), but this approach is limited by the dysphoric and sedative side effects of KOR activation. Different signaling pathways downstream of the KOR have been associated with different physiological outcomes, driving the development of "biased" agonists that preferentially signal through one pathway or another. This study examines the potential of biased agonism to treat AUD by correlating the pharmacological bias of different KOR-specific ligands with their effects on voluntary ethanol consumption in mice using a two bottle choice drinking paradigm.

Day 3 • July **24th**
Session #5, Talk #3
Kappa

11:20am – 11:30am

Sarah C. Simmons
Postdoctoral Researcher

Sarah C. Simmons*, Ryan D. Shepard, Shawn Gouty, Ludovic D. Langlois, Brian M. Cox and Fereshteh S. Nugent

Early life stress dysregulates kappa opioid receptor signaling within the lateral habenula

While there is evidence for direct dynorphin/kappa opioid receptor (DYN/KOR) regulation of the mesocorticolimbic system, to date there has been little study on KOR regulation of other important stress/mood-related regions such as the lateral habenula (LHb). Here we provide significant evidence for the presence of a functional DYN/KOR modulation of LHb activity through both intrinsic properties and synaptic modulation in discrete populations of LHb neurons identified by the presence of the hyperpolarization-activated current (Ih). Secondly, we found that severe early life stress dysregulated DYN/KOR signaling downstream from receptor signaling which resulted in blunted responses of LHb neurons to acute KOR stimulation. To our knowledge, this is the first study directly assessing the effects of DYN/KOR signaling on LHb neuronal excitability, and providing evidence for DYN/KOR dysregulation in the LHb following severe early life stress.

Day 3 • July **24th**
Session #5, Talk #4
Kappa

11:30am – 11:40am

Susan Ahmedyar
M.S. Candidate

Susan Ahmedyar*, Kabirullah Lutfy

The role of dynorphin/kappa-opioid receptor (DYN-KOR) system in stress-mediated affective disorders and alcohol self-administration in mice

In a preliminary study, we evaluated the impact of age and the role of DYN-KOR system in the development of negative affective states that occur following repeated variable stress exposure as well as in alcohol self-administration in female mice. Preprodynorphin null mice and their littermates/controls underwent a 10-day repeated variable stress exposure followed by alcohol self-administration in the home cage. Our results revealed that endogenous dynorphin plays a significant role in the development of depression-like behavior and alcohol self-administration in an age-related manner.

Day 3 • July 24th
Session #5, Talk #5
Kappa

11:40am – 11:50am

Danni Cao
Postdoctoral Researcher

Chongguang Chen, Danni Cao*, Lan Hsuan Melody Huang, Lee-Yuan Liu-Chen

Characterization of knockin mice harboring kappa opioid receptors (KOR)-inducible Cre recombinase (KOR-iCre), a better tool for precise localization of KOR-expressing neurons

We generated a knockin mouse line expressing an inducible Cre in the oprk1 gene (KOR-iCre), cross-bred with Ai6 mice and induced with tamoxifen in adulthood to enable expression of ZsGreen in cytosol of KOR cells. Three-dimensional images of CLARITY-cleared brains will be presented, which display high density of KOR-expressing cells in the claustrum, dorsal endopiriform nucleus, basolateral amygdala, prefrontal cortex, nucleus accumbens, substantia innominata and nucleus reunion, similar to distribution of KOR mRNA. The mouse line also facilitates precise identification of KOR-expressing cells at the cellular level. This KOR-iCre line is different from the previous KOR-Cre mouse line of S. Ross' lab., in which Cre is expressed constitutively in KOR cells and thus in all KOR-lineage cells, not just those expressing KOR in adulthood. This mouse line will be a valuable tool for investigation of KOR.

Day 3 • July 24th
Session #5, Talk #6
Kappa

11:50am – 12:00pm

Moriah L. Jacobson

Postdoctoral Researcher

Moriah L. Jacobson*, Sarah C. Simmons, Hildegard A. Wulf, Fereshteh S. Nugent, Caroline A. Browne, Irwin Lucki

Kappa Opioid Receptor Desensitization is Required for the Protracted Antidepressant Effects of Ketamine

We hypothesized that the kappa opioid receptor (KOR) system is necessary for ketamine to exert its rapid and sustained antidepressant activity. Our data demonstrate that 1) ketamine pretreatment prevents behavioral and electrophysiological responses caused by subsequent KOR activation, and 2) these responses in mice are prevented by prior KOR blockade. These studies provide evidence that ketamine reduces KOR signaling which may contribute to the protracted clinical antidepressant effects of ketamine.

Day 3 • July 24th
Session #5, Talk #7
Kappa

12:00pm – 12:10pm

Valentina Martinez Damonte

Postdoctoral Researcher

Valentina Martinez Damonte*, Julie Kauer

kORs in the VTA modulate GABAergic synaptic plasticity

We have previously identified kORs as key players in stress-induced alterations in VTA synaptic plasticity since a single acute exposure to cold-water swim stress blocks a form of potentiation of inhibitory postsynaptic currents (LTPGABA) on VTA dopaminergic cells due to a persistent, ligand-independent constitutive activation of kappa opioid receptors.
Both dopaminergic and non-dopaminergic cells in the VTA receive dynorphin inputs from different brain regions. Here, using a conditional knock out approach we selectively deleted kORs in dopaminergic neurons and found that this deletion did not prevent stress-induced block of LTPGABA. We have also begun to identify the specific GABAergic pathways to the VTA that exhibit this form of LTPGABA using optogenetics.
Our work contributes to the understanding of the effects of endogenous opioids within the VTA as well as the relevance of GABAergic modulation of the reward pathways.

Day 3 • July 24th
Session #5, Talk #8
Kappa

12:10pm – 12:20pm

Courtney A. Bouchet
Graduate Student

Courtney A. Bouchet*, Katherine L. Suchland, Susan L. Ingram

Differential effects of persistent inflammation on the presynaptic opioid and cannabinoid receptors within the ventrolateral periaqueductal gray

Opioids and cannabinoids are both used to treat pain; however, it is not well understand whether these systems function differently after pain. In these experiments, we use slice electrophysiology to determine functional changes in the presynaptic opioid and cannabinoid systems in the ventrolateral periaqueductal gray, a region of the descending pain modulatory pathway, after persistent inflammation in male and female Sprague Dawley rats. We find that persistent inflammation does not appear to effect the function of the presynaptic mu opioid receptor but induces plasticity in the cannabinoid system, reducing the function of the cannabinoid 1 receptor.

Day 3 • July 24th
Session #6, Talk #1
Pain

12:20pm – 12:30pm

Bryan Sears
Graduate Student

Bryan Sears*, Emily Jutkiewicz

Potential Involvement of Peripheral Opioid Receptors In The Development Of Tolerance To Morphine

Tolerance plagues the use of opioid analgesics but the mechanisms of tolerance are not fully understood. Here, we show the activation of opioid receptors in the peripheral nervous system is sufficient for inducing tolerance to the antinociceptive effects of morphine. Further, antagonism of peripheral opioid receptors with naloxone-methiodide attenuates the development of tolerance, suggesting the involvement of peripheral opioid receptors in tolerance development.

Day 3 • July 24th
Session #6, Talk #2
Pain

12:30pm – 12:40pm

Zachariah Bertels
Graduate Student

Zachariah Bertels*, Kendra Siegersma, Serapio M. Baca, Amynah Pradhan

A translationally significant model of migraine facilitation through chronic morphine is attenuated by PAC1 receptor antagonism

Migraine is an extremely common and debilitating disorder, which can be worsened through continued treatment with mu-opioid receptor agonists. Here we translated this phenomenon, in mice, in two mechanistically distinct models of migraine such that, repeated morphine treatment resulted in exacerbation of migraine correlates. Further, we found that this exacerbation of migraine could be reversed through antagonism of the primary PACAP receptor, PAC1, demonstrating the effectiveness of our model to not only translate a known human phenomenon, but also to successfully screen potential new therapeutic targets.

Day 3 • July **24th**
Session #6, Talk #3
Pain

12:40pm – 12:50pm

Evan F. Fullerton
Graduate Student

Evan F. Fullerton*, Myurajan Rubaharan, Mary C. Karom, and Anne Z. Murphy, PhD

The impact of advanced age on Mu Opioid Receptor signaling in the midbrain periaqueductal gray: implications on analgesia

Chronic pain is exceedingly prevalent in individuals over 65 years of age, but is under-managed in this population. We used cellular and pharmacological techniques to assess age-induced alterations in opioid binding and signaling in the midbrain ventrolateral periaqueductal gray of the rat, a critical region in the modulation of pain. Our novel findings elucidate the mechanisms responsible for reduced morphine potency in aged animals and identify potential therapeutic targets to improve pain management in the elderly.

Day 3 • July **24th**
Session #6, Talk #4
Pain

12:50pm – 1:00pm

Benjamin M. Clements

Graduate Student

BM Clements*, CD Peterson, KF Kitto, GL Wilcox, and CF Fairbanks

Influence of Strategically Substituted Agmatines on Opioid-Induced Neuroplasticity

Agmatine, an putative neurotransmitter, has been shown to reduce the negative side effects of opioids while enhancing opioid analgesia after exogenous administration. Due to a non-ideal CNS distribution and pharmacokinetic profile, we have developed a series of strategically substituted agmatines, designed for increased lipophilicity and brain penetration while maintaining the pharmacologic activity of agmatine. These strategically substituted agmatines prevent the development of chronic morphine tolerance after intrathecal and subcutaneous administration.

Day 3 • July 24th
Session #6, Talk #5
Pain

1:00pm – 1:10pm

Sarah Palumbo

Second Year Medical Student

Sarah A. Palumbo*, Kayleigh M. Adamson, Sarathbabu Krishnamurthy, Shivani Manoharan, Donielle Beiler, Anthony Seiwell, Colt Young, Raghu Metpally, Richard C. Crist, Glenn A. Doyle, Thomas N. Ferraro, Mingyao Li, Wade H. Berrettini, Janet D. Robishaw, Vanessa Troiani

Assessment of probable opioid use disorder using electronic health record documentation

In this retrospective, cross-sectional study, we demonstrated that a series of proxy measures for each of the DSM-5 criteria for Opioid Use Disorder (OUD) can be extracted through Electronic Health Record (EHR) review and further demonstrated increases in OUD prevalence and psychiatric comorbidities in patients that are part of a drug monitoring program. The use of proxy measures that rely on multiple sources of data, including prescription drug history and medical record notes, can help to identify patients with OUD that have not been diagnosed, as OUD is traditionally underdiagnosed from an analysis of ICD Codes. The development and implementation of precision medicine approaches could become a major factor in developing more efficient and personalized pain treatments with less risk for addiction, for which studies of this potential could be helped by establishing more effective proxy measures for OUD using EHR data.

Day 3 • July 24th
Session #6, Talk #6
Pain

1:10pm – 1:20pm

Tamara Markovic
Ph.D. Student

Tamara Markovic*, Nicolas Massaly, Christian Pedersen, Kavitha Abiraman, Jung Hoon Shin, Brian Ruyle, Yvan Vachez, Jeniffer Garcia, Veronica A. Alvarez, Michael R. Bruchas, Meaghan Creed and Jose A. Morón

Pain induces somatic adaptations in Ventral Tegmental Area Dopamine neurons to drive anhedonia-like behavior

Pain is a complex phenomenon composed of sensory and negative affective component, whose common characteristic is a decrease in motivation to initiate and complete goal-directed behavior. Using chemogenetics, fiber photometry, slice electrophysiology and voltammetry we found that pain decreases the activity of mesolimbic VTA DA neurons concurrent with reduced motivation for natural rewards which can be overcome by selective activation of VTA DA neurons, decreases spontaneous firing and intrinsic excitability of VTA DA neurons and leads to dysregulation of MOR system in the VTA. In conclusion, our findings reveal that somatic adaptations within VTA DA neurons underlie pain induced negative affect.

Day 3 • July 24th
Session #6, Talk #7
Pain

1:20pm – 1:30pm

Kylie B. McPherson
Ph.D. Candidate

Kylie B. McPherson*, Courtney A. Bouchet, and Susan L. Ingram

Changes in intrinsic properties of vlPAG neuron subtype after persistent inflammatory pain

Electrophysiological characterization of the vlPAG uncovered 4 cell types with distinct firing patterns. One of these 4 types exhibited enhanced basal activity after persistent inflammatory pain. Future directions will investigate the potential role of excitatory afferents in this enhanced activity as well as the presence of any alterations to synaptic machinery.

Day 3 • July 24th
Session #6, Talk #8
Pain

1:30pm – 1:40pm

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