Type them into questions box!

“Why am I muted?”
Don’t worry. Everyone is muted except the presenter and host.
Thank you and enjoy the show.

Contact ACS Webinars® at acswebinars@acs.org

Join a global community of over 150,000 chemistry professionals

Find the many benefits of ACS membership!

Benefits of ACS Membership

**Chemical & Engineering News (C&EN)**
The preeminent weekly digital and print news source.

**NEW! ACS SciFinder**
ACS Members receive 25 complimentary SciFinder® research activities per year.

**NEW! ACS Career Navigator**
Your source for leadership development, professional education, career services, and much more.


Contact ACS Webinars ® at acswebinars@acs.org
Celebrating 4 years & 40 Drug Discovery Webinars!

How has ACS Webinars benefited you?

"The drug delivery series from ACS Webinars has been very helpful to me. I have expanded my knowledge of the many types of drug delivery systems and different ways to formulate these systems. In addition, I have also learned what other labs and companies are doing in this field."

Fan of the Week

Alexa Barres, Graduate Student, Dissertator Status
Mecozzi Group, University of Wisconsin-Madison
ACS member 7 years strong!

Be a featured fan on an upcoming webinar! Write to us @ acswebinars@acs.org
Learn from the best and brightest minds in chemistry! Hundreds of webinars on diverse topics presented by experts in the chemical sciences and enterprise.

Recordings are an exclusive ACS member benefit and are made available to registrants via an email invitation once the recording has been edited and posted.

Live Broadcasts of ACS Webinars® continue to be available to the general public every Thursday from 2-3pm ET!

www.acs.org/acswebinars

An individual development planning tool for you!

ASSESS YOURSELF

STRENGTHEN YOUR SKILLS

SET GOALS

EXPLORE CAREERS

ChemIDP.org
Join the Division Today!

For $25 ($10 for students), You Will Receive:

- A free digital copy of our annual medicinal chemistry review volume (over 600 pages, $160 retail price)
- Abstracts of MEDI programming at national meetings
- Access to student travel grants and fellowships

Find out more about the ACS MEDI Division! www.acsmedchem.org
The Opioid Crisis and Quest for Superior Analgesics without Addiction

Slides available now and an invitation to view the recording will be sent when available.
www.acs.org/acswebinars

Co-produced with the ACS Division of Medicinal Chemistry
Outline

- Mechanics of the opioid crisis
- Why are opioids so dangerous?
- Pain transmission and mechanisms
- Strategies to develop next-gen pain therapy

The Clinical Problem – Pain!

- **Over 40% of all Americans** visit the clinic, every year, due to chronic pain (Arthritis, etc.)
- **504 billion dollars** are spent each year; lack of productivity and lifestyle (CDC)
- **Prototypic analgesics** in the clinic are opioids: Morphine, Codeine, Vicodin, etc.
Audience Challenge Question
ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

In 2016, approximately how many opioid prescriptions were written?

• 10 million
• 50 million
• 100 million
• 175 million
• Over 200 million

The Crisis in Numbers as of 2016 (CDC report)

• **11.5 million** people misused prescription opioids
• **2.1 million** misused prescription opioids for the first time
• **2.1 million** have opioid use disorder
• ~**116** overdose deaths every day in the U.S. (2016)
Salient Issues of the Opioid Crisis

Opioid OD deaths have become the #1 cause of accidental death in the US

Prescription opioids are the leading offenders — redirection, over-prescription, doctor shopping, etc

New highs
United States, drug overdose deaths*, monthly

https://www.economist.com/blogs/graphicdetail/2017/03/daily-chart-3

Opioid Receptors

Opioid receptors have been used as targets for developing analgesics for decades

Mu Opioid Receptor  Kappa Opioid Receptor  Delta Opioid Receptor

Class A, Rhodopsin type GPCRs: 60% homology
Current Opioids are Addictive Through the Same Mechanism

All opioid pain medications have the same target: the mu-opioid receptor
Mu-receptor activation leads to analgesia, **addiction and side effects**

- **brain:** Pain relief, **CNS side effects:** addiction & respiratory depression
- **spinal cord:** Pain relief
- **Periphery:** **Somatic side effects:** constipation, physical withdrawal, etc.

morphine, hydrocodone, etc.

Abuse Potential

- **Physical dependence** – withdrawal symptoms upon cessation, etc.
- **Drug seeking behaviors**
- **Reinforcement** – self-administration
Respiratory Depression

• The fatal side effect of narcotics – breathing stops once threshold is crossed

• Opioids activate neurons in the pre-bötzinger complex in the brainstem that regulates breathing

Extracted from: https://vimeo.com/229746641 and Miller et al., 2017 Anesthesiology dx.doi.org/10.1097/ALN.0000000000001719

Tolerance

• Repeated use of opioids reduces therapeutic effect over time

• Need to dose-escalate to get same analgesic (or euphoric) effects

• Tolerance to respiratory depression develops much slower – leads to OD situations!
Recent Policy Steps

• All opioids are Schedule II drugs in the U.S., making them difficult to prescribe
• Manufacturing caps are progressively limiting opioid availability
• Narcan (naloxone) – opioid antagonist to be made widely available to first-responders to tackle overdoses
• However, chronic/neuropathic pain markets remain major unmet needs

Audience Challenge Question

Which of these narcotic side effects is the main reason for overdose fatalities? (More than one correct answer may be possible)

• Physical dependence
• Tolerance
• Constipation
• None of the above
The Solution

- Equal or more efficacious compared to same dose of an opioid
  *low doses = less potential for side effects*
- CNS-acting to address chronic pain mechanisms
- No tolerance – no need to dose escalate for efficacy
- No narcotic CNS side effects – physical dependence, addiction
- No or reduced opioid peripheral side effects – constipation, etc.
- No respiratory depression – the reason for OD deaths

PAIN AND ITS TRANSMISSION
What is Pain?

• Pain is a cardinal sign that helps us perceive the environment
  
  – **Noxious pain** – early warning system
  
  – **Inflammatory pain** – hypersensitivity due to tissue damage and repair
  
  – **Pathological pain** – damage to nervous system (neuropathic pain) or abnormal function (dysfunctional pain)

---

**Simplified Model of Pain Transmission**

Scholz and Woolf, Nat Neuro 2002 doi:10.1038/nn942
Where Can We Intervene?

STRATEGIES TO DEVELOP NEXT-GEN PAIN THERAPY

A (very) brief overview

Yekkrala et al., 2017 Nat. Rev. Drug. Discov. doi:10.1038/nrd.2017.87
Ion Channels in Pain

• **Sodium channel ligands:** commonly used as local anesthetics (lidocaine, etc.)
  
  – Several subtype selective ligands are being developed
  – Recent success with VX-150 (Nav1.8 inhibitor, Vertex) in Phase 2 clinical trials

• **Potassium channel openers:** Kv7, K2P openers amongst other channels under pre-clinical development
Ion Channels in Pain

- **Calcium channel ligands**: Gabapentin (Pregabalin, Lyrica) is the prototypic analgesic with some efficacy in neuropathic pain
  - Z944 (Zalicus) and CNV2197944 (Convergence) currently in clinical trials

- **TRPV1 channel blockers** failed in the clinic due to increased body temperature
  - NEO6860, JNJ-38893777 and AZD1386 are now under investigation without thermal side effects

Disease-Modifiers

- **Anti-NGF antibodies** – tanezumab, fasinumab, etc relieve osteoarthritic pain in clinical trials.
  - Side effect included progression of arthritis!

- **Anti-cGRP drugs for migraine**
  - Novartis (erenumab), Teva (fremanezumab) are antibody therapeutics with positive phase III data
  - Ubrogepant is a cGRP receptor antagonist that also has positive phase III data
GPCR Targets

- G protein coupled receptors
- 7 transmembrane domains
- Three major types of G proteins act as second messengers
- Opioid, cannabinoid, angiotensin, chemokine receptors are some of the major pain GPCR targets

Abuse Deterrent Opioids

- Pill formulations that cannot be crushed or melted
- But the active drug are still opioids
- The side effects remain and studies show that they can exacerbate prescription abuse in certain cases (Kunins 2015 *JAMA Int. Med.* 175, 987–988, Cassidy et al., 2014 *Pain Med.* 15, 440–451)
- Opana ER was pulled from the market by the FDA
Biased Ligands

- Biased agonist – a ligand that activates the receptor selectively via particular signal transduction mechanisms

- Trevena's Oliceridine is a clinical stage example – activates G protein vs β- arrestin

- Hot field in GPCR research with implications in many diseases

Peripherally-Restricted Opioids

- Kappa opioid agonists produce pain relief

- Major use-limiting side effects include psychotomimetic effects (hallucinations), dysphoria, on top of narcotic effects

- Cara therapeutics is developing kappa agonists that do not penetrate the blood-brain barrier – peripherally-restricted

- CR845 currently in phase 2 clinical trials – failed to achieve primary end point in a osteoarthritis trial but other trials on-going
Central Sensitization

Under normal conditions, the stimulus determines the perception of touch vs. pain.

In chronic pain, nociceptors are sensitized – even non-noxious stimuli lead to pain perception.


A Safer Centrally Acting Painkiller is Needed

Blue181 targets a novel receptor predominantly in the spinal cord to produce analgesia without narcotic side effects.
Blue’s Approach is Informed by Novel Biology

Heteromers provide a refined combinatorial target space with new pharmacological properties.

Concepts of GPCR Heteromerization

Evidence for dimerization/oligomerization
1. Coimmunoprecipitation
2. BRET and FRET
3. Atomic-force microscopy
Understanding heteromers as drug targets

- Many opioids originally thought to target a single opioid receptor actually engage a range of both homomeric and heteromeric opioids receptors.

- Incorporating heteromer targeting information can help explain the pharmacology of current drugs, as well as create newer, more selective ones, engineered to be safe and effective.

Case study: morphine and fentanyl activity

- Morphine and fentanyl are widely considered prototypic mu agonists.

- However, the strongest activity for morphine and fentanyl is at mu-delta opioid receptor heteromers.

- Heteromers thus add an additional layer of complexity to the opioid system.


Morphine and fentanyl were tested for agonist activity at various opioid receptors expressed in HEK-293 cells using the intracellular calcium release method.
Selective antagonism of morphine and fentanyl at mu-delta heteromeric receptors

- Naltrindole (NTI), a selective delta antagonist, inhibits morphine- and fentanyl-induced calcium release via mu-delta heteromers
- Morphine and fentanyl are not inhibited by NTI at mu-mu homomers


Blocking **mu**-**delta** inhibits morphine and fentanyl analgesia in monkeys

- Morphine and Fentanyl were tested for analgesia in rhesus monkeys using the tail-flick method
- Naltrindole (NTI) strongly inhibits morphine and fentanyl in rhesus monkeys in a dose dependent manner (increasing doses of NTI moves the morphine/fentanyl dose-response to the right)
- These data (*taken together with slide 45*) clearly show that mu-delta opioid heteromers are responsible for the analgesia produced by these ligands even in monkeys.

Mu-delta opioid receptors also help to explain morphine side-effects, such as tolerance and dependence


**Blue181 is a First-in-Class Small Molecule**

Discovered via rational design & extensive SAR to be highly selective to mu-kappa heteromeric opioid receptor

It has sub-picomolar binding & activation potency for the receptor complex compared with other opioid receptors
Blue181 is a potent analgesic - mouse
with both IV and oral bioavailability

- Many painkiller candidates fail on efficacy
- Blue181 is 50x more potent than morphine in mice (i.v.)
- Blue181 is also orally active (ED$_{50}$ = 2.4 mg/kg)

Analgesia is measured by a tail flick test, where heat is applied to the tail of the mouse and the amount of time it takes to withdraw the tail is measured.

Blue181 is Non-Addictive in Animal Models

- no physical dependence
- no drug-seeking behavior

Physical dependence can be tested by administering naloxone to opioid-dependent mice. Naloxone blocks mu-opioid receptors and immediately reverses their effects. In mice, this withdrawal causes “jumping,” a symptom of physical dependence.

A conditioned place preference test is an industry standard assay to assess reward seeking or aversive behavior towards a drug, based on the amount of time the mouse spends in an area where it received the drug for multiple days.
Tolerance to Blue181 is Reduced or Absent

Tail-flick responsiveness following a single dose of Blue181 was measured in drug-naive mice (control, black line) and in mice given high-dose Blue181 for three days (blue line). No significant tolerance was detected, as the two curves for the groups were not significantly different.

- Morphine produces significant and rapid tolerance, limiting its use for chronic pain conditions
- Blue181 shows no tolerance when administered i.t. (spine)

Blue181 Produces No Respiratory Depression

Effects of Blue181 (blue) on breathing were tested via whole-body plethysmography with saline (black) and morphine (red) serving as controls. As expected, morphine produces significant respiratory depression within minutes, while saline and Blue181 produce no effects on breathing.

- Morphine and other opioids produce significant & rapid respiratory depression
- This is what makes opioid overdoses so deadly
- Blue181 produces no respiratory depression even at 800 x higher than the i.v. analgesic dose
Summary

• **Opioid crisis** is ballooning out of control

• The need to replace traditional opioid therapeutics is immediate
  – Narcotic side effects to avoid: tolerance, physical dependence, addiction, respiratory depression

• Several **promising** lines of investigation

• Tremendous opportunity for **novel chemistry**

Acknowledgements

• **Blue Tx Team**
  – David Roberson
  – Michio Painter
  – Phil Portoghese (U of MN)

• **Chris McCurdy** (U of FL)

• **Clifford Woolf** (Harvard and BCH)

• **Jane Aldrich** (our awesome moderator!)
The Opioid Crisis and Quest for Superior Analgesics without Addiction

Ajay Yekkirala
Co-Founder and Chief Scientific Officer, Blue Therapeutics

Jane Aldrich
Professor of Medicinal Chemistry, College of Pharmacy, University of Florida and Councilor, ACS Division of Medicinal Chemistry

Slides available now and an invitation to view the recording will be sent when available.
www.acs.org/acswinars

The Opioid Crisis and Quest for Superior Analgesics without Addiction

Join the Division Today!

For $25 ($10 for students), You Will Receive:

• A free digital copy of our annual medicinal chemistry review volume (over 600 pages, $160 retail price)
• Abstracts of MEDI programming at national meetings
• Access to student travel grants and fellowships

Find out more about the ACS MEDI Division! www.acsmedchem.org
Upcoming ACS Webinars

www.acs.org/acswebinars

Thursday, June 28, 2018

Pitfalls and Promise of Central Nervous System Drug Discovery
Co-produced with the ACS Division of Medicinal Chemistry and the American Association of Pharmaceutical Scientists

Expert

Valentin Gribkoff
TheraStat LLC
Yale University School of Medicine

Thursday, July 12, 2018

Become a Science Advocate: How to Engage Your Elected Officials
Co-produced with the External Affairs & Communications

Experts

Allison A. Campbell
Pacific Northwest National Laboratory

Laura Pence
University of Hartford

Contact ACS Webinars ® at acswebinars@acs.org

The Opioid Crisis and Quest for Superior Analgesics without Addiction

Ajay Yekkirala
Co-Founder and Chief Scientific Officer, Blue Therapeutics

Jane Aldrich
Professor of Medicinal Chemistry, College of Pharmacy, University of Florida and Councilor, ACS Division of Medicinal Chemistry

Slides available now and an invitation to view the recording will be sent when available.

www.acs.org/acswebinars

Co-produced with the ACS Division of Medicinal Chemistry
Celebrating 4 years & 40 Drug Discovery Webinars!


How has ACS Webinars® benefited you?

**KEY INSIGHT FROM OVER 40 WEBINARS**


“The drug delivery series from ACS Webinars has been very helpful to me. I have expanded my knowledge of the many types of drug delivery systems and different ways to formulate these systems. In addition, I have also learned what other labs and companies are doing in this field.”

**Fan of the Week**

Alexa Barres, Graduate Student, Dissertator Status
Mecozzi Group, University of Wisconsin-Madison
ACS member 7 years strong!

Be a featured fan on an upcoming webinar! Write to us @ acswebinars@acs.org
Benefits of ACS Membership

**Chemical & Engineering News (C&EN)**
The preeminent weekly digital and print news source.

**NEW! ACS SciFinder**
ACS Members receive 25 complimentary SciFinder® research activities per year.

**NEW! ACS Career Navigator**
Your source for leadership development, professional education, career services, and much more.

ACS Webinars® does not endorse any products or services. The views expressed in this presentation are those of the presenter and do not necessarily reflect the views or policies of the American Chemical Society.

Contact ACS Webinars ® at acswебinars@acs.org

Upcoming ACS Webinars
www.acs.org/acswebinars

Thursday, June 28, 2018
Pitfalls and Promise of Central Nervous System Drug Discovery
Co-produced with the ACS Division of Medicinal Chemistry and the American Association of Pharmaceutical Scientists

Expert
Valentin Gribkooff
TheraStat LLC
Yale University School of Medicine

Thursday, July 12, 2018
Become a Science Advocate: How to Engage Your Elected Officials
Co-produced with the External Affairs & Communications

Experts
Allison A. Campbell
Pacific Northwest National Laboratory

Laura Pence
University of Hartford

Contact ACS Webinars ® at acswебinars@acs.org